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INTRAVENOUS INJECTION OF HYPOTONIC SALT SOLUTION CONTAINING SULFANILAMIDE FOR STREPTOCOCCIC MENINGITIS

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The advent of sulfanilamide has revolutionized the treatment of meningitis caused by Streptococcus haemolyticus beta. Previously the disease had a mortality of about 97 per cent; this drug is said to have reduced the mortality to about 20 per cent. Endeavors now are aimed toward the establishment of the proper dosage and the development of the best method of administering the drug.

There are two objectives in the treatment of the meningitides: the saving of life and the prevention of the sequelae which often develop. If one investigates a series of persons who four or five years previously had cerebrospinal meningitis which was treated by serum, one finds a high percentage of serious sequelae, such as jacksonian epilepsy, deafness and severe headaches. These sequelae are caused by deformity of the pia-arachnoid which results from repair of the acute inflammation or by internal hydrocephalus due to partial or complete block in the circulation of the cerebrospinal fluid. It is not known as yet what the later results may be in cases of streptococcic meningitis cured by sulfanilamide. It is desirable, therefore, to use the method of administration of this drug which will reduce the inflammation most quickly.

It has been shown by Long and Bliss [1] that whether sulfanilamide is given by mouth or by subcutaneous or intravenous injection, the concentrations in the cerebrospinal fluid are practically the same in all cases and the concentrations in the blood stream are constantly higher than those in the cerebrospinal fluid. They concluded that, provided the drug is well absorbed from the gastrointestinal tract, the results are as good when sulfanilamide is given by mouth, the usual method in cases of meningitis, as when it is injected. Most clinicians give the drug by subcutaneous injection also. Intrathecal injections have been used, but as they are not entirely free from danger most physicians feel that they are not desirable.

Prior to the use of sulfanilamide there was no satisfactory treatment for suppurative meningitis. Intravenous injection of hypotonic solutions

1. Long, P. H., and Bliss, E.: Para-Amino-Benzene-Sulfonamide and Its Derivatives, J. A. M. A. **108**:32 (Jan. 2) 1937.

of sodium chloride and free drainage of cerebrospinal fluid were employed in many cases. There was an occasional recovery, but the vast majority of the patients died. However, in practically all of these cases of meningitis the patients did show considerable clinical improvement for a time. In other words, this treatment did favorably modify the disease, but not sufficiently to effect recovery. I have personally treated 24 patients with various types of suppurative meningitis by this method; most of them showed clinical improvement, but none recovered. In 1935 I wrote, ". . . perivascular drainage, in its present form at least, is not a cure for septic meningitis." [2]

When a hypotonic solution of sodium chloride is given intravenously, the osmotic pressure of the blood stream is reduced. This causes a continuous flow of fluid from the capillaries into the pericellular tissue spaces of the central nervous system. The permeability of the capillaries is increased in inflamed tissue. I have been able to show that when a hypotonic solution of sodium chloride is injected intravenously the decreased osmotic pressure of the blood stream is exerted principally at the point of least resistance, i. e., at the capillary walls in inflamed tissue.[2] When such solutions are given to patients suffering from meningitis, there results a continuous passage of fluid through the capillaries of the inflamed tissue in the central nervous system and through the pericellular fluid spaces. Part of this fluid passes down the Virchow-Robins perivascular spaces, augmenting the lake of cerebrospinal fluid. Finally it is largely reabsorbed into the blood stream from the venous capillaries. Sulfanilamide easily permeates animal membrane, and, if added to the hypotonic solution of sodium chloride under the conditions just cited, it will be carried through the inflamed areas.

Experiments were planned to determine whether giving sulfanilamide intravenously in a hypotonic solution of sodium chloride has the advantage of increasing the concentration of the drug in the cerebrospinal fluid.

EXPERIMENTS

Experiment 1.—On April 23, 1937, monkey 68, weighing 4.7 Kg. and having a temperature of 37.2 C. (99 F.), was given an intravenous injection of a 0.425 per cent solution of sodium chloride containing 1.12 Gm. of sulfanilamide per liter. The injection was given over a period of nine hours and ten minutes, at the rate of 22 cc. per kilogram each hour. It was begun at 3:10 p. m. Specimens of blood and of cerebrospinal fluid were removed coincidentally at 5:30 p. m., 8:40 p. m. and 12:20 a. m. Determinations of the percentage of sulfanilamide in these specimens are shown in figure 1. The percentage was definitely greater in the blood than in the cerebrospinal fluid. Twelve hours and five minutes after the first injection was ended a second was begun on the same animal, the same solution being given at the same rate. Determinations made on the blood and on the cerebrospinal fluid at 2:20 p. m., 5:10 p. m. and 12 m. are also shown in figure 1.

2. Retan, G. M.: Development of Therapeutic Use of Forced Perivascular (Spinal) Drainage, J. A. M. A. **105**:1333 (Oct. 26) 1935.

It will be seen that the percentage of sulfanilamide is distinctly greater in the cerebrospinal fluid than in the blood in the last 2 specimens.

Experiment 2.—For three successive days, beginning April 26, monkey 58, weighing 3.2 Kg. and having a temperature of 38.8 C. (101.8 F.), was given an intravenous injection of a physiologic (0.85 per cent) solution of sodium chloride containing 0.817 Gm. of sulfanilamide per liter. On the fourth day was injected a 0.375 per cent solution of sodium chloride containing 0.817 Gm. of sulfanilamide per liter. The duration of the injections and the periods between them are shown in figure 2. At intervals, determinations of the percentage of sulfanilamide in the blood and in the cerebrospinal fluid were made coincidentally. Results of these determinations are shown in figure 2. At no time during the injection of the physiologic solution of sodium chloride was the concentration of sulfanilamide greater in the cerebrospinal fluid than in the blood. However, when the 0.375 per cent solution of sodium chloride was given there was a shift to a higher percentage of sulfanilamide in the cerebrospinal fluid than in the blood.

Experiment 3.—On May 6 at 8 a. m. monkey 57, weighing 2.95 Kg. and having a temperature of 37.7 C. (99.9 F.), was given 1.23 Gm. of sulfanilamide in 123 cc. of water by stomach tube. Four hours later, at 12 m., an intravenous injection of a 0.375 per cent solution of sodium chloride containing 1.23 Gm. of sulfanilamide per liter was begun. This injection was given at the rate of 22 cc. per kilogram each hour. Determinations of the sulfanilamide content of the blood and of the cerebrospinal fluid were made at intervals, as shown in figure 3. There was a shift in the two later fractions to a higher percentage of sulfanilamide in the cerebrospinal fluid than in the blood.

Experiment 4.—On May 12 at 10 a. m. monkey 63, weighing 3.3 Kg. and having a temperature of 38.8 C. (101.8 F.), was given by mouth a capsule containing 0.66 Gm. of sulfanilamide. At 11:20 a. m. an intravenous injection of a 0.375 per cent solution of sodium chloride containing 0.66 Gm. of sulfanilamide per liter was given at the rate of 22 cc. per kilogram each hour. In figure 4 is shown the relation of the percentage of sulfanilamide in the blood and the percentage in the cerebrospinal fluid. Here again was found a shift to a higher percentage in the cerebrospinal fluid in the later fractions.

These various experiments were repeated several times and in each instance the same results were obtained. The following conclusions are therefore justified:

1. When a physiologic solution of sodium chloride containing sulfanilamide is given to monkeys intravenously, the concentrations of sulfanilamide are greater in the blood than in the cerebrospinal fluid.

2. When a hypotonic solution of sodium chloride containing sulfanilamide is injected intravenously, the concentrations during the first injection are the same as with the physiologic solution. However, if the injection of a hypotonic solution is repeated on the second day, there occurs a shift to a higher percentage of sulfanilamide in the cerebrospinal fluid than is contained in the blood.

3. A similar shift to higher concentrations in the cerebrospinal fluid than in the blood can be produced by giving the drug by mouth in solution or in capsules prior to the intravenous injection of a hypotonic solution of sodium chloride.

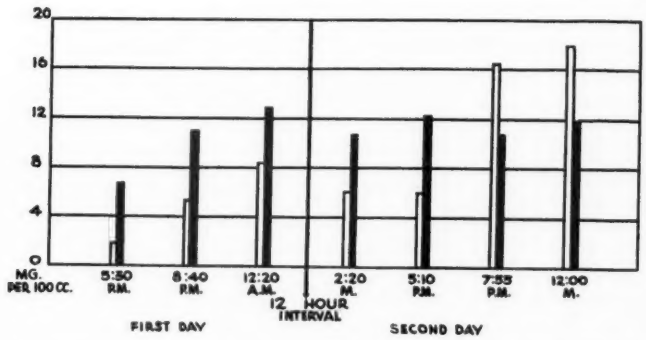

Fig. 1 (Experiment 1).—Light bars show the concentration of sulfanilamide in the cerebrospinal fluid in milligrams per hundred cubic centimeters. Dark bars show the concentration in the blood. Each set of determinations was made coincidentally. A 0.425 per cent solution of sodium chloride containing 1.25 Gm. of sulfanilamide per liter was injected intravenously. On the first day the percentage remained higher in the blood. When this injection was repeated on the following day there was a shift to a higher concentration in the cerebrospinal fluid than in the blood.

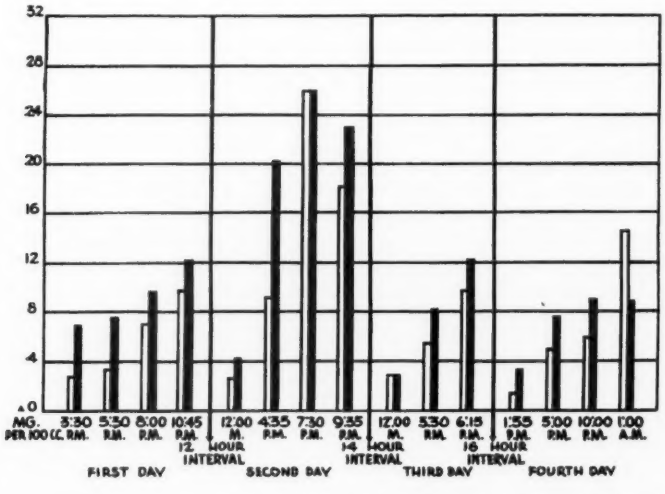

Fig. 2 (Experiment 2).—Light bars show the concentration of sulfanilamide in the cerebrospinal fluid in milligrams per hundred cubic centimeters. Dark bars show the concentration in the blood. Each set of determinations was made coincidentally. A solution of 0.817 Gm. of sulfanilamide per liter was injected in 0.85 per cent sodium chloride on four subsequent days. During the injection on the first three days at no time did the concentration of sulfanilamide in the cerebrospinal fluid exceed that in the blood. On the fourth day the solution was changed to 0.375 per cent sodium chloride containing 0.817 Gm. of sulfanilamide per liter. Observe the shift to a higher concentration of sulfanilamide in the cerebrospinal fluid than in the blood.

4. The shift just mentioned depends on two factors: the presence of sulfanilamide in the tissues of the body and the intravenous introduction of a hypotonic solution of sodium chloride containing sulfanilamide.

These experiments therefore establish a rationale for the use of intravenous injections of a hypotonic solution of sodium chloride containing

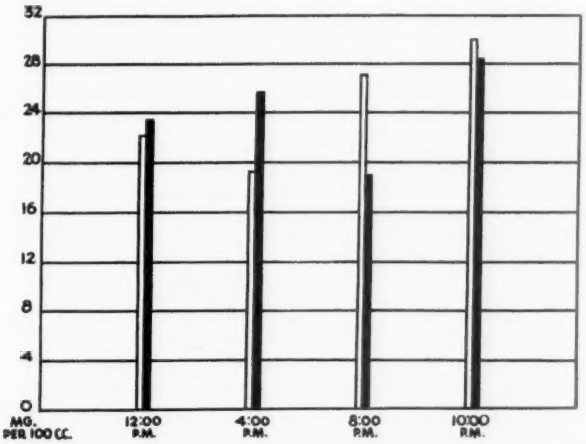

Fig. 3 (Experiment 3).—Light bars show the concentration of sulfanilamide in the cerebrospinal fluid in milligrams per hundred cubic centimeters. Dark bars show the concentration in the blood. Each set of determinations was made coincidentally. This chart shows the shift to a higher percentage of sulfanilamide in the cerebrospinal fluid than was found in the blood when 1.23 Gm. of sulfanilamide was given in solution by stomach tube four hours prior to the intravenous injection of 0.375 per cent solution of sodium chloride containing sulfanilamide.

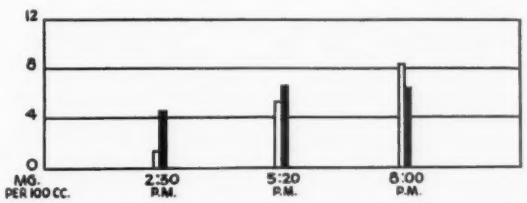

Fig. 4 (Experiment 4).—Light bars show the concentration of sulfanilamide in the cerebrospinal fluid in milligrams per hundred cubic centimeters. Dark bars show the concentration in the blood. Each set of determinations was made coincidentally. This chart shows that the same shift to higher concentrations in the cerebrospinal fluid than in the blood is produced when sulfanilamide is given by capsule prior to the intravenous injection of 0.375 per cent solution of sodium chloride containing sulfanilamide.

sulfanilamide in the treatment of those types of infection of the central nervous system for which sulfanilamide has been shown to be useful.

REPORT OF A CASE

R. S., a boy aged 16 years and weighing 70 Kg., was admitted to the Syracuse Memorial Hospital on April 15, 1937. The past history was not pertinent.

The present illness began with a sore throat. On April 10 earache developed with spontaneous rupture of the left ear drum. On April 13 the boy had pain and tenderness over the left mastoid. On April 14 severe headache and irritability developed, and on April 15, when he was seen by Dr. Dye, he complained of severe headache and vomiting. The temperature was 104 F.; the pulse rate was 60. There was marked rigidity of the back and neck; Kernig's sign was elicited, and the pupils were unequal. There was a purulent discharge from the left ear. The patient entered the hospital at 4 p. m., appearing acutely ill. The temperature was 103 F., the pulse rate 60 and the respiratory rate 20. The boy was unable to urinate. Examination showed marked rigidity of the neck and back. There was a positive Kernig reaction. The right pupil was dilated; both pupils reacted to light and in accommodation; there was bilateral nystagmus both to the right and to the left. The fundi and disks were normal and the margins clearcut; there was slight physiologic cupping, and the retinal veins were dilated. Except for the purulent discharge from the ear and tenderness over the mastoid, physical examination gave negative findings. Lumbar puncture showed a pressure of 20 mm. of mercury. There were 2,960 cells per cubic millimeter of fluid, with 13 per cent lymphocytes and 87 per cent polymorphonuclear leukocytes. No organisms were seen on a direct smear. Culture yielded beta hemolytic streptococci. Analysis of the blood showed the hemoglobin content to be 95 per cent, red cell count 5,000,000 and white cell count 25,900, with polymorphonuclears 89 per cent and monocytes 11 per cent. The urine contained a few pus cells and red blood cells, a moderate number of granular and hyaline casts, mucus and bacteria. At this time 3 Gm. of sulfanilamide was given by mouth. Between 4 and 8 p. m. the boy's condition became progressively worse. He exhibited periodic twitchings of the muscles of the hands and arms and slight mental confusion. At 8:25 p. m. he was given his first intravenous injection of hypotonic solution of sodium chloride. The details of the treatment are shown in the figures. However, the facts of the greatest interest are as follows: One hour after the beginning of the injection of the hypotonic salt solution containing sulfanilamide, the patient stated that he was feeling a great deal better. His mind was completely clear, and the periodic muscular twitchings had ceased. On April 16 at 7:10 a. m., four hours after the completion of this intravenous injection, Dr. O'Connor performed a simple mastoidectomy, with removal of the tegmen antri forward to the tegmen tympani, freely exposing the dura of the midcranial fossa in this area. At 8 a. m. the patient was returned to his room in good condition. Fifteen hundred cubic centimeters of a physiologic solution of sodium chloride was given by clysis. Three grams of sulfanilamide was given every four hours during the day. At 3 p. m. there was marked cyanosis of the lips and nail beds.

Four hours after the operation the patient's condition was good; he was conscious and was taking fluids by mouth. At 9:45 a. m. he was conscious. He urinated voluntarily and was taking fluids, and there was no vomiting. From 1:45 to 6:25 p. m. his condition grew progressively worse; drowsiness and wandering delirium developed. At this time a second intravenous injection of a hypotonic solution of sodium chloride containing sulfanilamide was given. Again, about an hour after the beginning of the intravenous injection, the patient stated that he was feeling fine. His mind was perfectly clear. The intravenous injection was completed at 12:40 a. m. on April 17. At 4:30 a. m. the boy again became confused

and delirious. At 10:15 a. m. a third injection was given, for five hours. A third time the patient showed definite clinical improvement within an hour after the beginning of the intravenous injection, and for a third time he stated that he was much improved. After this the patient received two intravenous injections of hypotonic solution of sodium chloride with sulfanilamide, the fourth on April 18 and the fifth on April 19. During this time his mind remained completely clear. The pupils were equal and reacted normally. On April 19 there was no rigidity of the neck or back, even on extreme anterior flexion. On April 20 physical examination gave completely negative results. On April 21 the patient sat up in bed to eat his meals and he had at that time completely recovered. One gram of sulfanilamide, the last dose, was given on April 20.

The urine was reported to be normal after the second intravenous injection.

My associates and I are not in a position to know what result we should have obtained in this case had we given sulfanilamide by mouth

Experimental Data in a Case of Hemolytic Streptococcic Meningitis

		Sulfanilamide in Cerebrospinal Fluid (Mg. per 100 Cc.)					
Date 1937	Treatment Number	Original Fluid	First Hour	Second Hour	Third Hour	Fourth Hour	Fifth Hour
4/15	1	1.000	1.176	3.180	4.610	5.985	6.995
4/16	2	8.130	8.545	10.415	10.990	13.070	13.070
4/17	3	10.640	15.420	12.040	21.430	20.840	.....
4/18	4	10.690	13.790	14.810	15.380	16.260	18.870
4/19	5	12.050	13.630	14.080	10.870	11.760	13.060

		Cerebrospinal Fluid			Sulfanilamide in 24 Hours (Gm.)		0.425% Solution of Sodium Chloride	
Date 1937	Treatment Number	Count	Lymphocytes	Polymorphonuclears	Oral	Intravenous	Hr.	Cc.
4/15	1	2,960	13	87	3.0	10	5	2,200
4/16	2	2,488	78	22	6.0	10	4½	1,750
4/17	3	2,311	55	45	4.3	8	5	2,000
4/18	4	890	86	14	2.6	6	5	2,950
4/19	5	223	97	3	3.3	6	5	2,400
4/20	6	133	94	6	1.0	..	..	.....
4/21	7	44	100	0	0.0	..	..	.....

and by subcutaneous injection without using injections of hypotonic solution of sodium chloride containing sulfanilamide. However, every one who saw the patient was impressed by the prompt subjective and objective improvement shown within an hour of the beginning of each intravenous injection. I believe that this method of treatment is based on sound theoretic grounds, and I am presenting the case to encourage its trial in cases of meningitis in which sulfanilamide can be used and in which the patients are not progressing favorably under other treatment.

It would seem that the doses of sulfanilamide used in the intravenous solution in this case were unnecessarily large, as the concentrations found in the cerebropsinal fluid were higher than my associates and I believe to be necessary. A great deal more experience will be necessary before we are able to determine the best dosage of this drug. In the next case in which I use this treatment I plan to give about half as

much sulfanilamide in the hypotonic solution. However, there were no harmful results. An alkaline powder of calcium carbonate and sodium bicarbonate was given at intervals of four hours.

PROCEDURE

Lumbar Puncture.—This is done with the patient in the usual position on a Bradford frame. He is then rotated so that he comes to rest on his back, with the needle protruding through the window of the frame. The puncture is made through the midline, in either the third or the fourth lumbar interspace. Here the intraspinous ligament lends aid in holding the needle in situ. A small amount of cerebrospinal fluid (not over 5 cc.) is removed for laboratory examination. When the patient is delirious, strips of adhesive tape are placed around the chest and the pelvis and fastened to the frame to prevent displacement of the needle by sudden movement on the part of the patient (fig. 5). After the cerebrospinal fluid for laboratory testing has been removed, the stylet is replaced in the lumbar puncture needle. The stylet should be bent slightly to prevent its slipping from place.

Intravenous Injection.—In using this treatment expert technic is imperative. When selecting a needle, the physician must bear in mind the rate at which he intends to administer the injection. Either a no. 18 or a no. 19 needle will allow a rate of flow of the solution as rapid as is ever advised. A no. 20 needle will rarely admit a liter of solution an hour, and a no. 21 may be used if the rate is to be less than 500 cc. each hour. The intravenous injection may be given in any vein in which a needle can be inserted. The best veins, of course, are those of the cubital space or the internal saphenous vein. If one of the veins of the arm is to be used, it is wise first to bandage the arm to a restraining board. One of the most important factors in successful intravenous injection is the introduction of the needle well into the vein. After the arm is bandaged to the board, the skin is sterilized at the site of the injection with iodine and alcohol. A tourniquet is then applied above the site of injection. A blood pressure cuff is the best tourniquet. By inflating the cuff to a level between the systolic and the diastolic pressure, one obtains the best filling of the vein. A well filled vein is the first requisite to good intravenous technic. The vein is then held firmly by the thumb below the site of the injection. This will prevent rolling of the vein during the introduction of the needle. After the needle pierces the skin and the point is engaged in the wall of the vein, it is forced through the wall and pushed well into the vein. The tourniquet is released, and the intravenous tube is connected with the needle. Both needle and rubber tubing are fastenend to the skin by adhesive tape, a little play being allowed in the rubber tube so that any subsequent movement of the extremity will not dislodge the needle (fig. 6).

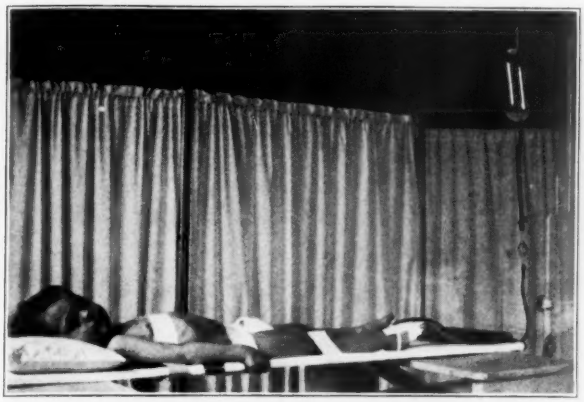

Fig. 5.—Child on a Bradford frame prepared for treatment. Lumbar puncture has been done, and the lumbar needle protrudes through a window in the Bradford frame. Adhesive straps are used as shown in the illustration when the child is delirious.

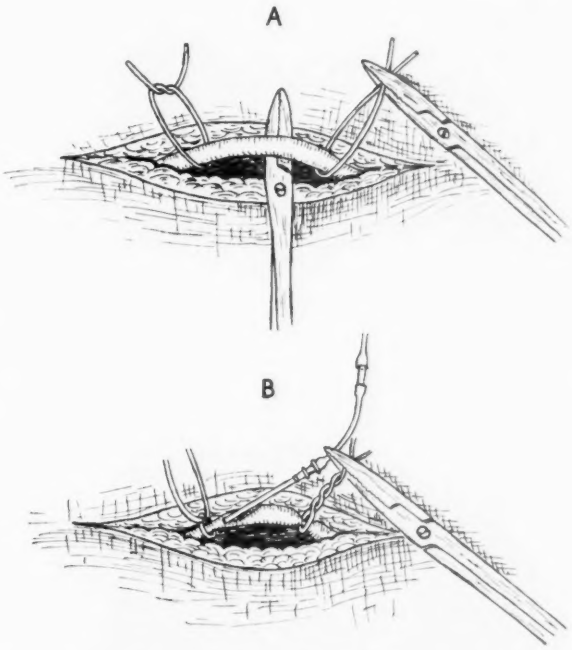

Fig. 6.—Method of tying in the intravenous cannula with the lower suture twisted and not tied. At the completion of the treatment these sutures are removed, the wound closed by clips and pressure applied by a bandage to stop any bleeding. In subsequent treatments the same opening in the vein can be used, often as many as three or four times.

It is often necessary in small children to cut down on the vein and tie the needle in. The internal saphenous vein is the one of choice in this procedure; it will be found between the internal malleolus of the tibia and the tendon of the tibialis anticus muscle. One of the veins of the arm may be used. It is desirable not to tie off the vein below the point where the cannula is introduced, in order that it may be preserved for future use. Two sutures are placed around the vein, one above and the other below the site at which the cannula is to be introduced. A single knot is tied in the upper suture, a loop being left. The ends of the lower suture are clamped and can be twisted to prevent bleeding. The vein is then nicked between the sutures, and the cannula is introduced. The knot in the upper suture is drawn tightly around the needle (fig. 6*B*). At the completion of the intravenous injection, the suture is removed and a tight compress applied. This will result in the least possible damage to the vein, so that it may be used for subsequent treatments.

The rate of injection most successfully used is 10 cc. of solution each hour per pound of body weight (22 cc. per kilogram each hour). However, more than 1 liter an hour should not be given. This rule is practically invariable in cases of acute poliomyelitis and acute encephalitis, except that during the last hour of a five hour treatment the rate may sometimes be reduced.[3] However, in cases of septic meningitis, especially when there is a complication of acute nephritis, as in the case reported here, a slower rate of injection must be adopted.

The strength of solution found to be the most effective is 0.375 per cent sodium chloride.

Treatments of five hours' duration, with rest intervals of several hours between treatments, are advised.

Cerebrospinal fluid is released from the lumbar puncture needle during the intravenous injection for the purpose of relieving increased intracranial pressure, and for no other reason. Drainage of cerebrospinal fluid is not in itself a successful therapeutic procedure in the treatment of any type of infection of the central nervous system. There is no relation between the amount of cerebrospinal fluid drained and the therapeutic result. It is impossible to advise the amount of fluid to be removed, since the pressure and the replacement of fluid vary considerably in individual cases as well as in the same case during various periods of treatment. If the fluid is under considerable pressure and is spurting from the needle, it is wise to drain from 5 to 10 cc. during a half-hour period. If the fluid is dripping rapidly, less than this amount should be drained (not over 5 cc.). If the fluid emerges from the needle by a slow drop, the stylet should be replaced at once without

3. Retan, G. M.: J. Pediat. **11**:647 (Nov.) 1937.

draining any fluid. If too much cerebrospinal fluid is removed, headache will develop. This headache will disappear within ten to fifteen minutes if no cerebrospinal fluid is allowed to drain.

The drainage of too great an amount of cerebrospinal fluid during the intravenous injection of a hypotonic solution of sodium chloride can result in cerebellar herniation. If the directions just given are carried out, such an accident cannot occur.

The laboratory work described in this article was done in the College of Applied Science at Syracuse University under the sponsorship of Chancellor Graham. The work was further made possible by the contributions of Dean Paul Shipman Andrews, Mr. Hurlburt W. Smith, Mr. Oscar Soule, Mr. Frederick Barker, Mrs. Martin H. Knapp, Mr. Samuel H. Cook and Mr. A. L. Kronquest, Syracuse, N. Y.; Mrs. S. Foster Hunt, Providence, R. I., and Mr. G. F. Morrison and Mr. Bernard S. Barron, New York.

459 James Street.

EFFECT OF A MILK SUPPLEMENT ON THE PHYSICAL STATUS OF INSTITUTIONAL CHILDREN

II. OSSIFICATION OF THE BONES OF THE WRIST

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ROCK HILL, S. C.
AND
LYDIA J. ROBERTS, PH.D.
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Ossification in the wrist and forearm has been widely used by anatomists, educators and other investigators as an index of anatomic age. As such, it has been correlated with mental age, the intelligence quotient and other factors, and important conclusions have been drawn from the findings. Only rarely has the suggestion been made that this index might be modified by the state of nutrition, although it seems almost self evident that any prolonged deficiency or marked improvement in the diet would have an appreciable effect on development of bone.

The present study was prompted by the desire to study this question under experimental conditions. An excellent opportunity was presented to do this in connection with a larger study, which was being carried out in a children's institution.[1] The purpose of the project was to determine whether an increase in the amount of milk consumed to make a total of approximately 1 quart (946 cc.) daily per child would produce any measurable improvement in the physical status of the children in a year's time and whether any advantage could be demonstrated for irradiated over nonirradiated milk.

EXPERIMENTAL PROCEDURE

Subjects.—As indicated in a preceding article,[1] the subjects comprised all the residents in an institution caring for approximately 150 children. The ages ranged from 1 to 15 years, but the large majority of the children were of grade school age. At the beginning of the experimental year three groups were set up; they were as nearly alike as possible as to age, sex and nutritional status, as judged by height, weight and condition of the teeth.. The control group continued to receive the

From the Department of Home Economics of the University of Chicago.

The expenses of this investigation were defrayed in part by the Irradiated Evaporated Milk Institute.

1. Roberts, L. J.; Blair, R.; Lenning, B., and Scott, M.: Effect of a Milk Supplement on the Physical Status of Institutional Children: I. Growth in Height and in Weight, Am. J. Dis. Child. **56**:287 (Aug.) 1938.

institutional diet; one group was given an additional pint (473 cc.) equivalent of evaporated milk, and the third group was given an equal amount of irradiated evaporated milk.

Area Chosen for Study.—The wrist was chosen as the portion of the skeleton in which to follow osseous development. This is a justifiable procedure, since ossification of the bones of the wrist has been shown by numerous workers to be representative of development in other centers (Pryor,[2] Rotch,[3] Baldwin, Busby and Garside,[4] Wallis [5]). This does not mean that development will be precisely the same throughout the body but merely that if ossification is accelerated or retarded in the wrist it will be correspondingly accelerated or retarded elsewhere. In comparing the progress of these three groups of children it seems reasonable, then, to assume that the rate of development of the carpal bones can be considered indicative of the stage of development throughout the skeleton. Both Todd [6] and Wallis [5] have suggested that other centers of ossification, the knee, for example, may be better indicators at certain stages; but for the entire period of growth from birth to maturity, development of the carpal bones and of the epiphyses of the hand and wrist provides a complete scale, correlating with that of the epiphyses elsewhere. Two additional reasons for using the hand were the greater practical ease of taking roentgenograms of this area and especially the fact that the norms for skeletal development now available for comparison are based on measurement of these centers of ossification.

Roentgenograms.—Roentgenograms of the right hands were taken with a Ritter portable x-ray machine. Great care was exercised to have the hands and arms in a uniform position in order that all roentgenograms would be strictly comparable. In each case the hand and the greater part of the forearm were placed on a table, with the hand in the roentgen field and against the film holder. The fingers were held together; the thumb was slightly and naturally extended. The middle finger the third metacarpal bone and the long axis of the forearm were in alinement. With this position, the upper surface of the lower part of the forearm was practically parallel with the surface of the table. Even slight rotation changes the profile of the radial and ulnar epiphyses and also the position and visible area of the carpal bones. The position described gives the broadest shadows of these

2. Pryor, J. W.: Development of the Bones of the Hand, Bull. State Coll. Kentucky, June 1905; Some Observations on the Ossification of Bones of the Hand, Bull. Univ. Kentucky **8**:67, 1916; Roentgenographic Investigation of the Time Element in Ossification, Am. J. Roentgenol. **29**:798 (June) 1933.

3. Rotch, T. M.: Roentgen Ray Methods Applied to the Grading of Early Life, Phys. Educ. Rev. **15**:396, 1910.

4. Baldwin, B. T.: Physical Growth of Children from Birth to Maturity, Iowa City, University of Iowa Press, 1921, chap. 7. Baldwin, B. T.; Busby, L. M., and Garside, H. V.: Anatomic Growth of Children, Iowa City, University of Iowa Press, 1928, p. 88.

5. Wallis, R. S.: How Children Grow, Iowa City, University of Iowa Press, 1931, p. 137.

6. Todd, T. W.: (*a*) The Skeleton, in Growth and Development of the Child: II. Anatomy and Physiology, White House Conference on Child Health and Protection, New York, Century Company, 1932, pp. 46-90; (*b*) Roentgenographic Appraisement of Developmental Growth in the Skeleton, in Growth and Development of the Child: IV. Appraisement of the Child, ibid., pp. 258-285; (*c*) Bodily Expression of Human Growth and Welfare, Science **82**:181 (Aug. 30) 1935.

bones. In the case of a few children, notably several extremely thin ones, whose wrists were difficult to put into the correct position, the arm and hand were held in place during the exposure. After development, all roentgenograms were examined carefully, and any doubtful ones were retaken. By this method roentgenograms were taken of all children at the beginning and at the end of the experimental year.

Measuring the Progress in Osseous Development.—A number of methods of determining the stage of osseous development were available, several, as that of Prescott [6d] having norms, derived from measurements for large numbers of children. The two chosen for use in this study were the Flory inspectional age scale [7] and the Carter index, or ossification ratio.[8] The Flory scale was used primarily for matching children in the several groups at the beginning. This is an inspectional age scale which measures qualitative as well as quantitative aspects of development. The inspectional method was the earliest one to be used for expressing anatomic age. Pryor, in 1905, prepared a chronologic time table for the appearance of the epiphyses and the development of the carpal bones. As early as 1908 Rotch suggested that a series such as that of Pryor might be of considerable value in assessing anatomic age. He proposed using the development of the carpal bones and of the epiphyses of the radius and the ulna for the period from infancy to puberty and the ossification and union of epiphyses of the radius, the ulna, the metacarpal bones and, in succession, the phalanges for the period from adolescence to maturity. Woodrow and Lowell [9] and Smith [10] also described the successive changes of the carpal bones and epiphyses in the growing hand, but they did not set up norms that could be used by other workers. Todd described more specifically [11] a time table for the appearance of the ossification centers, rate of spread of ossification and union of epiphyses not only in the bones of the hand and forearm but also in those of the knee, ankle and foot.

Flory extended and systematized descriptions for the inspectional method as applied to one of these areas, that is, to the hand and forearm.[7] He used for this purpose approximately 3,000 roentgenograms of the hands of children of the University of Chicago Laboratory Schools and of other children of similar socioeconomic status.[12] From these records he chose a typical roentgenogram of the

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6d. Prescott, D. A.: Determination of Anatomical Age in School Children and Its Relation to Mental Development, Cambridge, Harvard University Press, 1923.

7. Flory, C. D.: Osseous Development in the Hand as an Index of Skeletal Development, Monograph 3, Society for Research in Child Development, Washington, D. C., National Research Council, 1936, p. 41.

8. (*a*) Freeman, F. N., and Carter, T. M.: A New Measurement of the Development of the Carpal Bones and Its Relation to Physical and Mental Development, J. Educ. Psychol. **15**:257, 1924. (*b*) Carter, T. M.: Technique and Devices Used in Radiographic Study of the Wrist Bones of Children, ibid. **17**:237, 1926.

9. Woodrow, H. H.: Brightness and Dullness in Children, Philadelphia, J. B. Lippincott Company, 1919, pp. 97-122. Woodrow, H. H., and Lowell, F.: Various Indices of Anatomic Age, Pedagog. Semin. **29**:1, 1922.

10. Smith, H. W., and Rotch, T. M.: Method of Roentgenographic Age Determination, U. S. Nav. M. Bull. **7**:20, 1913.

11. Todd.[6a, b]

12. One hundred in each age and sex group for the ages from 8 to 17 years; from 67 to 100 for the ages from 5 to 7 years and, from 30 to 36 for the age of 4 years.

right hand for each age and sex from birth to 20 years and then prepared a detailed description of the characteristics most typical of each stage of development. These descriptions concern not only carpal bones and radial and ulnar epiphyses but all epiphyses in the hand as well. They take into account, therefore, all types of changes which various authors have considered significant in assessing development. These typical roentgenograms together with the detailed descriptions constitute a series of norms for skeletal development. By comparison with these standards a particular child may be given an inspectional age, namely, that of the roentgenogram to which his own mostly closely corresponds. This scale is obviously to a considerable extent subjective and has therefore some of the disadvantages of any subjective measure. Flory has expressed the belief, however (and experience in this study has confirmed his belief), that when a roentgenogram may be directly compared with the standard roentgenogram typical of each age as well as with the accompanying description, much of the subjectivity is ruled out. For showing qualitative as well as quantitative growth the method has decided advantages.

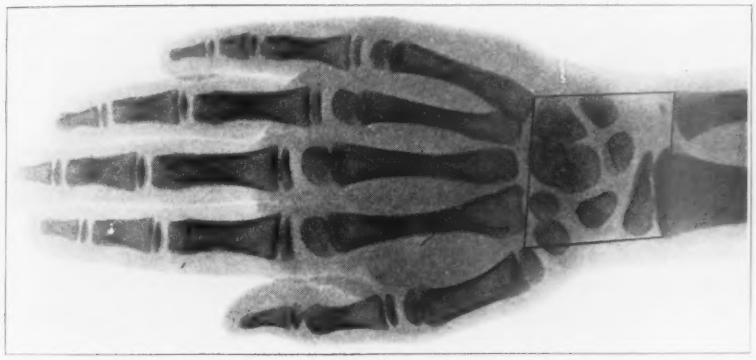

Fig. 1.—Roentgenogram of the hand of a girl 7 years and 5 months old, showing the outline of the area circumscribed for the Carter quadrilateral.

The Carter index was used for comparing the rate of ossification in the three dietary groups. This method was first described by Freeman and Carter, in 1924.[8a] It relates the sum of the areas of the shadows of the carpal bones and of the epiphyses of the radius and the ulna as actually measured by a planimeter to the area of the wrist (fig. 1), that is, it relates the area already ossified to the area to be ossified.

$$\frac{\text{Ossified area}}{\text{Area of carpal quadrilateral}} = \text{Ossification ratio}$$

Norms of osseous development for each age and sex were prepared by this method from examination of roentgenograms of children in the University of Chicago Laboratory Schools. Flory has recently revised these norms (using children in the same school) by greatly extending the number of children. These ratios make it possible to express the degree of development of the bones of the wrist in terms of its relation to the norm for age and sex and to compare children objectively with each other in this respect. Successive roentgenograms of the same child will show his increments of osseous growth, and these increments may be compared with those to be expected for his age, as indicated by the standards, as well as with those of other children. The statistical data here presented are

based on the Carter method of determining anatomic development. It was chosen because it is an objective method derived from a study of large numbers of children of a similar socioeconomic group, the units are small, the ratios are obtained by direct measurement and differences in growth are apparent in figures of appreciable size.

The Flory inspectional age scale was used and was found invaluable in placing children in order of developmental age and in matching children for the three groups. Partners were thus chosen on the basis of qualitative development in the whole hand as well as quantitative growth. Differences due to experimental procedure were determined by measuring the area of the wrist at the beginning and at the end of the year; these are expressed as differences between the increments of osseous growth so obtained.

In making the measurements for the present study a film was placed on a specially constructed light-box, and a polar planimeter was used in measuring the areas of the carpal bones and of the quadrilateral of the wrist for the Carter index. The planimeter is an ingenious device for measuring irregular areas of plane surfaces (as in maps). The polar planimeter, as here used, consists of two arms (the pole arm and the tracer arm) and the carriage. The tracer arm runs on a measuring wheel the movement of which is directly proportional to the area of the plane surface circumscribed by the tracer point. An attached vernier permits reading to the nearest hundredth of a square inch (0.06 sq. cm.). The area is recorded as the difference between the initial and the final reading. Measurements of the magnitude of the carpal areas can be duplicated easily by different trained observers and by the same person rereading the roentgenograms after an interval of several months.

In our study every precaution was taken to secure accurate measurements. All films were measured by the same person (V. MacN.), who acquired facility by checking with 2 experienced persons and who repeatedly tested her consistency and accuracy by rechecking her previous measurements. In order to minimize errors in measuring small bones or very irregular ones, the boundaries of these were traced three times, and the sum obtained was divided by 3. All measurements of the quadrilateral were also checked. As a final check on both measurer and recorder, each completed set of measurements on a roentgenogram was scanned for reasonableness of areas as judged by inspection of the bones and their relative size. To rule out any possible effect of the subjective element, all measurements were made and the indexes were computed and recorded with no knowledge on the part of the worker as to whose roentgenogram was being evaluated.

In order to determine the status of a particular child, it was necessary to interpolate, in the center scale, index values or ossification ratios for months of the year. The roentgenograms were taken for all children at the beginning and at the end of the experimental year and only incidentally near birthdays. It was necessary to be able to compare the figures for a child directly, whatever the number of months since his last birthday, with the standards. The interpolations made such comparisons possible.

Matching the Groups.—Although the initial roentgenograms were taken at the beginning of the study, almost simultaneously with other measurements, they could not be used in setting up the three groups for the study. This was true because, first, the technic of measuring and interpreting the films had to be mastered and, second, the measurements had to be made, several months elapsing before these tasks were accomplished. The three groups therefore had to be set up on other bases, as already described, and the supplementation was started long before the initial roentgenograms had been measured. There remained of these three groups

at the end of the study 35 controls, 37 children given milk and 36 given vitamin D milk, a total of 108. For some comparisons this initial grouping was used to assess the progress in anatomic development with which this article is concerned. It was clear, however, that a better comparison could be made for children matched on the basis of their initial anatomic age. After the first roentgenograms were developed and measured, therefore, the children were rematched as well as possible by stage of osseous development, all children being kept, of course, in their original dietary groups.

In selecting the new sets the Flory inspectional age was the chief criterion used; it was fortified by the Carter index and the chronologic age. Trios were formed by selecting from each of the original dietary groups a child matching those from the other 2 in skeletal months by the Flory standard, that is, a child at the same stage of development toward the mature form. The partners also were selected so that the age according to the Carter index and the chronologic age were the same or nearly so. In most cases all three criteria showed the ages of the 3 matched children to be within six months of each other; in others the ages were the same according to two criteria (one of them the Flory inspectional age) and were not far apart by the third. The Flory standard emphasizes develop-

TABLE 1.—*Comparison of the Three Matched Dietary Groups at the Beginning of the Experiment*

Group	Mean Chronologic Age		Mean Carter Index		Flory Inspectional Age, Mean Skeletal Months	
	Boys	Girls	Boys	Girls	Boys	Girls
Control	10.30	9.00	62.3	66.6	113	98
Plain milk	10.00	9.10	61.1	66.4	112	100
D milk	10.25	8.80	63.0	65.4	113	99

ment; the Carter index, growth in size of the ossified area. When these and the chronologic age were similar for a set of 3 children, it was judged that the trio were as nearly as possible in the same phase of growth at the beginning of the year. There were 24 sets of 3 children who could be thus matched and who remained till the end of the year. That the three groups made up from these matched trios were similar in osseous development is shown in table 1. The Carter index and the Flory inspectional age are remarkably alike for the matched dietary groups, and chronologic age, which was given less consideration in matching, agrees within a third of a year. A comparison of the progress of these three groups during the year should then be the best test of the effect of the dietary supplement on anatomic development.

RESULTS

As a result of obtaining measurements by means of the procedures which have been described, there were available for comparison Carter ossification ratios for 108 children at the beginning and at the end of the year. This includes the selected group of 72 children, 24 in each dietary group, who were initially matched as to sex and stage of osseous development. It is now of interest to examine the progress made by these children in a year, to determine whether there was any significant

TABLE 2.—*Deviation from Carter Indexes for all Matched Children at the Beginning and at the End of the Study and Changes During the Year in Relation to the Mean Index for Age and Sex and in Relation to Expected Gains*

No.	Sex	Carter Index at Beginning	Mean Index for Age	Deviation at Beginning: Points	Deviation at Beginning: Percentage	Carter Index at End	Mean Index for Age	Deviation at End: Points	Deviation at End: Percentage	Changes in Deviation from Mean for Age: Points	Changes in Deviation from Mean for Age: Percentage	Gain in Score for Year: Actual	Gain in Score for Year: Expected	Percentage of Expected Gain
Control group														
1	F	19	32	—13	—41	24	39	—15	—39	— 2	+ 2	5	7	71
2	F	51	62	—11	—18	60	72	—12	—17	— 1	+ 1	9	10	90
3	F	59	65	— 6	— 9	75	76	— 1	— 1	+ 5	+ 8	16	11	146
4	F	95	86	+ 9	+11	98	94	+ 4	+ 4	— 5	— 6	3	8	38
5	F	73	89	—16	—18	81	97	—16	—16	0	+ 2	8	8	100
6	F	80	96	—16	—17	91	103	—12	—12	+ 4	+ 5	11	7	157
7	F	89	96	— 7	— 7	94	102	— 8	— 8	— 1	— 1	5	6	83
8	M	24	27	— 3	—11	29	31	— 2	— 6	+ 1	+ 5	5	4	125
9	M	41	45	— 4	— 9	46	53	— 7	—13	— 3	— 4	5	8	63
10	M	37	55	—18	—33	42	63	—21	—33	— 3	0	5	8	63
11	M	41	60	—19	—32	49	69	—20	—29	— 1	— 3	8	9	89
12	M	61	63	— 2	— 3	63	71	— 8	—11	— 6	— 8	2	8	25
13	M	57	59	— 2	— 3	65	69	— 4	— 6	— 2	— 3	8	10	80
14	M	67	70	— 3	— 4	71	77	— 6	— 8	— 3	— 4	4	7	57
15	M	66	65	+ 1	+ 2	72	73	— 1	— 1	— 2	— 3	6	8	75
16	M	73	76	— 3	— 4	76	85	— 9	—11	— 6	— 7	3	9	33
17	M	82	87	— 5	— 6	100	96	+ 4	+ 4	+ 9	+10	18	9	200
18	M	79	89	—10	—11	78	98	—20	—20	—10	— 9	—1	9	—11
19	M	86	94	— 8	— 8	87	101	—14	—14	— 6	— 6	1	7	14
20	M	95	106	—11	—10	99	110	—11	—10	0	0	4	4	100
21	M	23	35	—12	—34	31	44	—13	—30	— 1	+ 4	8	9	89
22	M	48	67	—19	—28	52	74	—22	—30	— 3	— 2	4	7	57
23	M	77	96	—19	—20	82	102	—20	—20	— 1	0	5	6	83
24	M	102	104	— 2	— 2	104	108	— 4	— 4	— 2	— 2	2	4	50
Total		1,725	1,724	—199		1,669	1,907	—238		—39		144	183	
Group receiving plain milk														
1	F	28	35	— 7	—20	32	43	—11	—26	— 4	— 6	4	8	50
2	F	50	63	—13	—21	59	73	—14	—19	— 1	+ 2	9	10	90
3	F	58	70	—12	—17	67	79	—12	—15	0	+ 2	9	9	100
4	F	90	103	—13	—13	100	106	— 6	— 6	+ 7	+ 7	10	3	333
5	F	78	94	—16	—17	100	101	— 1	— 1	+15	+16	22	7	314
6	F	76	78	— 2	— 3	86	87	— 1	— 1	+ 1	+ 2	10	9	111
7	F	85	84	+ 1	+ 1	90	92	— 2	— 2	— 3	— 3	5	8	63
8	M	18	25	— 7	—28	24	30	— 6	—20	+ 1	+ 8	6	5	120
9	M	33	42	— 9	—21	37	50	—13	—26	— 4	— 5	4	8	50
10	M	42	52	—10	—19	55	60	— 5	— 8	+ 5	+11	13	8	162
11	M	46	54	— 8	—15	56	62	— 6	—10	+ 2	+ 5	10	8	125
12	M	50	71	—21	—30	60	78	—18	—23	+ 3	+ 7	10	7	143
13	M	58	63	— 5	— 8	67	71	— 4	— 6	+ 1	+ 2	9	8	112
14	M	67	71	— 4	— 6	70	78	— 8	—10	— 4	— 4	3	7	43
15	M	51	71	—20	—28	58	78	—20	—26	0	+ 2	7	7	100
16	M	60	82	—22	—27	76	92	—16	—17	+ 6	+10	16	10	160
17	M	81	94	—13	—14	85	101	—16	—16	— 3	— 2	4	7	57
18	M	79	78	+ 1	+ 1	85	88	— 3	— 3	— 4	— 4	6	10	60
19	M	87	92	— 5	— 5	96	99	— 3	— 3	+ 2	+ 2	9	7	129
20	M	101	100	+ 1	+ 1	105	105	0	0	— 1	— 1	4	5	80
21	M	23	30	— 7	—23	26	35	— 9	—26	— 2	— 3	3	5	60
22	M	52	49	+ 3	+ 6	58	57	+ 1	+ 2	— 2	— 4	6	8	75
23	M	99	106	— 7	— 7	108	110	— 2	— 2	+ 5	+ 5	9	4	225
24	M	91	99	— 8	— 8	102	104	— 2	— 2	+ 6	+ 6	11	5	220
Total		1,503	1,706	—203		1,702	1,879	—177		+26	+55	199	173	
Group receiving D milk														
1	F	29	35	— 6	—17	33	43	—10	—23	— 4	— 6	4	8	50
2	F	50	63	—13	—21	61	72	—11	—15	+ 2	+ 6	11	9	122
3	F	54	61	— 7	—12	67	71	— 4	— 6	+ 3	+ 6	13	10	130
4	F	95	101	— 6	— 6	99	105	— 6	— 6	0	0	4	4	100
5	F	70	86	—16	—19	81	94	—13	—14	+ 3	+ 5	11	8	138
6	F	83	77	+ 6	+ 8	93	86	+ 7	+ 8	+ 1	0	10	9	111
7	F	77	89	—12	—14	99	97	+ 2	+ 2	+14	+16	22	8	275
8	M	21	28	— 7	—25	25	32	— 7	—22	0	+ 3	4	4	100
9	M	29	35	— 6	—17	38	44	— 6	—14	0	+ 3	9	9	100
10	M	45	65	—20	—31	48	73	—25	—34	— 5	— 3	3	8	38
11	M	50	63	—13	—21	55	71	—16	—23	— 3	— 2	5	8	63
12	M	64	63	+ 1	+ 2	69	71	— 2	— 3	— 3	— 5	5	8	63
13	M	59	68	— 9	—13	70	75	— 5	— 7	+ 4	+ 6	11	7	157
14	M	64	71	— 7	—10	78	79	— 1	— 1	+ 6	+ 9	14	8	175
15	M	64	71	— 7	—10	67	79	—12	—13	— 5	— 3	3	8	38
16	M	64	68	— 4	— 6	70	74	— 4	— 5	0	+ 1	6	6	100
17	M	81	97	—16	—17	85	102	—17	—17	— 1	0	4	5	80
18	M	78	97	—19	—20	89	103	—14	—14	+ 5	+ 6	11	6	183
19	M	84	87	— 3	— 3	92	96	— 4	— 4	— 1	— 1	8	9	89
20	M	95	107	—12	—11	102	110	— 8	— 7	+ 4	+ 4	7	3	233
21	M	27	45	—18	—36	33	53	—20	—38	— 2	— 2	6	8	75
22	M	49	43	+ 6	+14	59	51	+ 8	+16	+ 2	+ 2	10	8	125
23	M	92	101	— 9	— 9	96	106	—10	— 9	— 1	0	4	5	80
24	M	102	101	+ 1	+ 1	113	106	+ 7	+ 7	+ 6	+ 6	11	5	220
Total		1,526	1,722	—196		1,722	1,893	—171		+25		196	171	

difference in rate of development between the groups receiving a supplement and the group not receiving one. The data obtained have been subjected to a number of comparisons. These have been made both for all the 108 children and for the 24 matched sets of 3 each. Since the matched sets provide the most reliable material, the comparisons for these will be given major consideration; the data for the 108 children will be used for confirmatory evidence.

TABLE 3.—*Percentage of Children in Matched Groups Having the Specified Relation to the Mean at the Beginning and at the End of the Year by Dietary Groups*

Group	Even with Mean or Above				Less Than 10 per Cent Below Mean				10 per Cent or More Below Mean			
	Beginning		End		Beginning		End		Beginning		End	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Control	2	8	2	8	10	42	7	29	12	50	15	63
Plain milk	4	17	2	8	6	25	10	42	14	58	12	50
D milk	4	17	4	17	4	17	9	38	16	67	11	46

TABLE 4.—*Change in Status in Relation to the Carter Mean During the Year by Dietary Groups*

Change in Carter Points	Control		Plain Milk		D Milk	
	No.	%	No.	%	No.	%
In more favorable relation to mean	4	17	12	50	11	46
By 5 or more points	2		6		4	
By 1-4 points	2		6		7	
In same relation to mean	2	8	2	8	4	17
In less favorable relation to mean	18	75	10	42	9	37
By 1-4 points	13		10		7	
By 5 or more points	5		..		2	

TABLE 5.—*Summary of Changes Made During the Year by Each of the Three Matched Dietary Groups Considered as a Unit*

Group	Deviation from Carter Mean				Total Points of Change in Deviation	Gain in Carter Points		Expected Gain		Actual Gain Over Expected Gain, %
	Beginning		End			Total Points	Mean	Total Points	Mean	
	Total Points	%	Total Points	%						
Control	−199	−11.5	−238	−12.5	−39	144	6.0	183	7.6	78.7
Plain milk	−203	−11.9	−177	− 9.4	+26	199	8.3	173	7.2	115.0
D milk	−196	−11.4	−171	− 9.0	+25	196	8.2	171	7.1	115.0

Change in Relation to the Carter Mean for Age.—In table 2 are given for each child the Carter ossification ratios at the beginning and at the end of the year, the deviation of these from the mean Carter index for age and sex and the gains made for the year. The first feature which strikes the eye is that with few exceptions all children

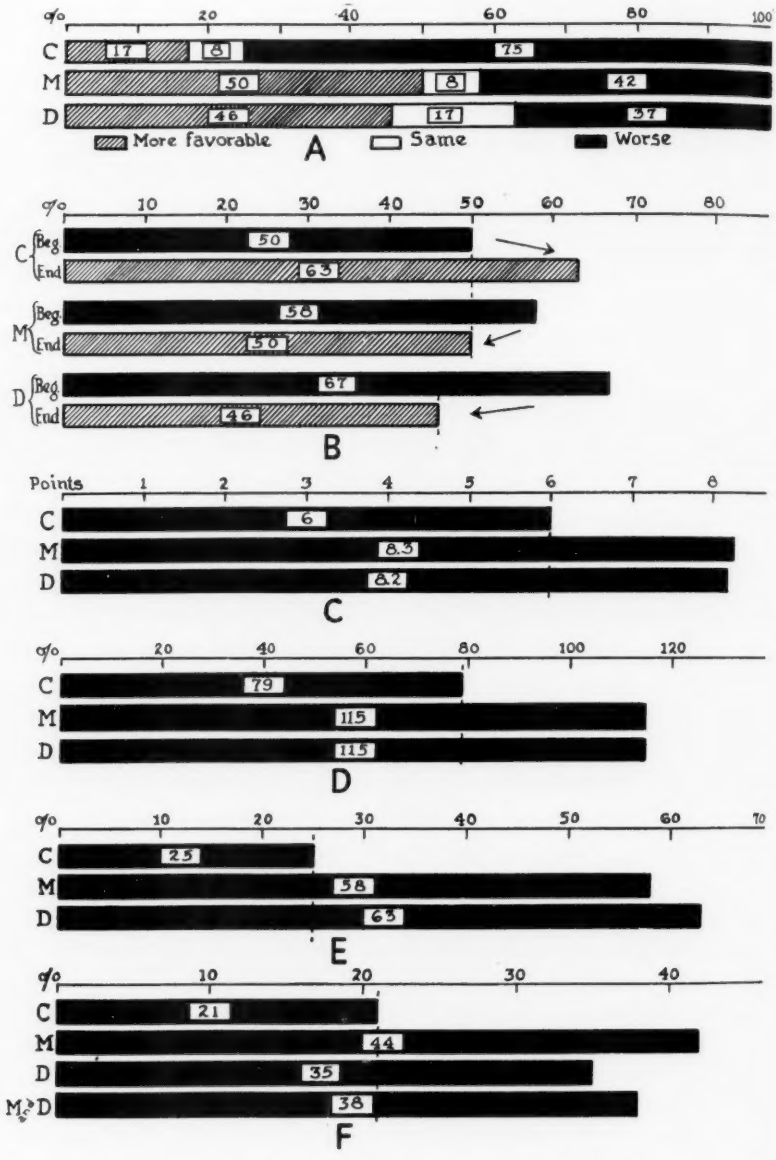

Fig. 2.—*A*, percentage of each group with a more favorable, the same or a worse relation to the norms at the end than at the beginning of the experimental year. *B*, percentage of each group 10 per cent or more below the norms at the beginning and at the end of the year. *C*, mean gain in Carter points. *D*, percentage of the expected gain made by each group. *E*, percentage of children in each group who made the expected gain or better. *F*, percentage of times in the matched trios a control child, one given milk and one given D milk, made the best gain during the year.

in all three groups were below the average in osseous development for their age, as judged by the Carter norms, both at the beginning and at the end of the year. Some of these negative differences were not large, but, as seen in table 3, over half the children at the outset were more than 10 per cent below the mean. The control group had some advantage in this respect, since only 50 per cent of these children, as compared with 58 and 67 per cent of the milk and of the D milk group, respectively, deviated as much as this from the average on their initial measurements. Taking each dietary group as a whole, however (table 5), the percentages of deviation from the mean were similar; 11.5 for the control, 11.9 for the plain milk and 11.4 for the irradiated milk group.

But how did the same groups stand at the end of the year? It is apparent from the summary in tables 3 to 5 that although all groups were still below the average the control group lost ground while the groups receiving a supplement reduced their deficits appreciably. Considering at first only whether individual children were better or worse off in this respect, it is found (table 4, fig. 2 *A*) that only 17 per cent of the control group improved their status, 8 per cent held their own and 75 per cent actually lost ground; that is, they were farther below the norms for their age at the end of the year than at the beginning. The milk groups fared better; 50 per cent of the children given plain milk and 46 per cent of those given D milk improved their status, and 42 and 37 per cent, respectively, were in less favorable relation to their means than they were at the beginning. When the size as well as the direction of these differences is considered, it is found that more children in the milk groups than in the control group have made gains of significant size. The percentage of children who reduced their deficits by 5 points or more was 8 for the control, 25 for the milk and 17 for the D milk group (table 4). The result of these larger gains by the milk groups is also seen in a shift in the percentage of children with negative deviations of 10 per cent or more from the standard. As seen in table 3 and figure 2 *B*, the percentage of children in the control group deviating as much as 10 per cent increased from 50 to 63, while it decreased from 58 to 50 for the plain milk group and from 67 to 46 for the D milk group.

A more precise method of comparison concerns the actual gain in the mean Carter ossification ratio made by each group during the year and its relation to the expected amount. In table 5 and figure 2 *C* it is seen that the mean advance in Carter points was 6 for the control, 8.3 for the plain milk and 8.2 for the D milk group. These differences of 2.3 and 2.2 Carter points in favor of the children given a supplement

are the equivalent of approximately one third of a year's expected quota. This will be referred to again in connection with the matched trios.

The same relation is shown when each group is considered as a unit and its total gains are compared with the expected gains by the Carter standards (table 5, fig. 2*D*). The control group made but 79 per cent of its expected quota, while both the milk groups gained 115 per cent of their expected amounts. While the control group, then,

TABLE 6.—*Percentage of Matched Children Making the Specified Percentage of Expected Gains in Carter Points for the Year by Dietary Groups*

Amount of Gain	Control		Milk		D Milk	
	No.	%	No.	%	No.	%
100% of expected gain or more	6	25	14	58	15	62.5
200% or more	1		4		3	
100-199%	5		10		12	
Less than expected gain	18	75	10	42	9	37.5
Some gain	17		10		9	
No gain	1		..		..	

did not quite hold its own, the groups given a supplement stored a balance to their credit which helped to make up some of their arrears.

When individual children are considered (table 6, fig. 2*E*) it is found that only 25 per cent of the controls as compared with 58 and 63 per cent, respectively, of the milk groups gained the expected amount or more during the year. Moreover, a larger number of the gains of 200 per cent of the expected or better were made by the children given milk, and the only case of failure of the carpal bones to keep up with the growth in the wrist was that of a control child.

TABLE 7.—*Number of Times in Twenty-Four Matched Trios the Specified Partner Made the Best Gain*

Child in Trio Making Best Gain	Number of Times	Percentage
Control	5.0	21.0
One or both partners receiving milk	19.0	79.0
Plain milk	10.5*	44.0
D milk	8.5*	35.0
Both partners receiving milk	9.0	37.5

* The milk partners showed the same values in one comparison.

One final comparison should be made on the basis of relative gains of individuals in the matched trios. This is obviously the most severe test of the efficacy of the supplement. Although the children in a given trio were closely alike at the outset as to their stage of osseous development and the dietary supplement was the only known variable that was introduced, it is obvious that many other factors which might affect

individuals in a group (such as colds or other illnesses or supplementary food brought by visitors) might obscure the effects of a specific experimental variable. It would hardly be expected, then, that in every trio the results would be sharply in favor of the children receiving the supplement, even though it may have had a favorable influence. It is of interest to note, nevertheless, how the partners in the several trios fared. Taking first the matter of relative gains, it is observed (table 7, fig. 2*F*) that in the 24 comparisons the control child was the best of the 3 in the gains he made 5 times while the child given plain milk was best 10½ times and the one given D milk 8½ times (the 2 partners given milk were the same in 1 comparison). That is, the control child was best in 21 per cent, the child given plain milk in 44 per cent and the child given D milk in 35 per cent of the comparisons. Both children given milk were better than the control partner in the trio 9 times, or in 37.5 per cent of the comparisons.

But the amount of the superiority should also be considered. This can best be determined by a comparison of the gain made on their means during the year by the partners in the matched trios. For example, in trio 4, table 2, the control child deviated from the mean for her age at the beginning by +9 points and at the end by +4 points. Her change in relation to the mean for her age was therefore —5 points. In similar manner, her partner who received plain milk is shown to have changed status by +7 points and the partner who received D milk by 0 point. A direct comparison can thus be made of the change in status during the year for the children given plain milk and D milk in each set with that of their control partners. For the previously described trio these differences are +12 points for the partner who received plain milk over the control and +5 points for the partner who received D milk over the control. The differences for partners in all 24 trios can be similarly obtained, and the average of these differences for each comparison can be determined (that is, between the partner who received plain milk and the control, the partner who received D milk and the control, and between the partners receiving milk).

By this method the mean of the differences between those receiving plain milk and the control partners is found to be 2.7 Carter points; the same difference is found for those receiving D milk and control partners. This is equivalent to 37 per cent of the mean expected gain for the year (7.3 Carter points) for the 72 children in the 24 trios. The difference between the plain milk and the D milk group is insignificant: 0.04 ± 0.9 point. It will be noted that this comparison of matched partners results in a larger difference between the groups given a supplement and the control group than was previously reported (table 5) as difference in mean gain. This apparent discrepancy is not real, since

the two procedures are measuring somewhat different factors. The previous figures for amount of superiority of the milk groups in osseous development (2.3 and 2.2 points) were obtained from average gains in the ossification ratio of the groups as a whole treated as random samples. This gives an approximate measure of the relative progress, which can be depicted graphically in a chart. By the latter comparison the ossification ratio is related to the Carter index for age and the expected gain for each partner. This increases the accuracy of the evaluation of the change, since it relates the change to a particular phase of growth. Still more important, it takes account of the fact that these were matched partners instead of children selected at random. This mean of the differences found from comparison of partners is therefore the most direct and accurate measure of real differences. The superiority of 2.7 Carter points for the partners who received milk over the controls obtained by this method is thus a more precise indication of the result of the experimental procedure than the 2.3 and 2.2 Carter points found for mean difference in "raw scores."

TABLE 8.—*Progress in Osseous Growth of One Hundred and Eight Children by Dietary Groups During the Experimental Year*

Item	Control	Milk	D Milk
Number of children	35	37	36
Percentage of children who are in a more favorable position in respect to the mean Carter index for age	26	54	41
Percentage of children 10 per cent or more below the mean:			
Beginning	54	43	61
End	60	38	47
Average gain for group:			
In Carter points	6.5	7.8	7.2
Percentage of expected gain	84	114	109
Percentage of children making expected gain or more	31	59	58

The differences between the milk groups and the control group are significant, since the ratio of the mean of the differences to its probable error is 3.23 for the group receiving plain milk over the control group and 3.47 for the group receiving D milk over the control group. This means that the chances are about thirty-three to one and fifty-five to one, respectively, that the differences are not due to chance and may be attributed to the milk supplement. Moreover, since all other differences found tend in the same direction, there is added assurance that the amount of the superiority of the groups given a supplement over the group not given one, that is, approximately one third of a year's expected quota of gain in ossification ratio, is significant.

Confirmatory Evidence from the Entire Group.—Though the data on the matched groups are the most reliable, it is of interest to note the extent to which those for the entire group of 108 children are in agreement. For economy of space only the most pertinent data have

been summarized in table 8. The results entirely confirm those for the matched groups. By every method of comparison the children given a supplement show on the average a somewhat greater advance in osseous development during the year than do the children not given a supplement.

Taking the results of all comparisons, then, both for the 24 matched trios and for the entire group, it is clear that, regardless of the method of analysis used, the milk groups seem to have excelled in measurable degree the control children in their rate of osseous development, as indicated by the increase of ossification in the carpal bones. The differences tend consistently in the same direction, in favor of the milk groups. Although their superiority is not great, the differences are of such size that, associated with this consistency of direction, they justify the conclusion that they are significant and can reasonably be attributed to the dietary supplement. The differences between the milk groups were small, variable in direction and insignificant. These results are moreover in agreement with those for height and weight, which were reported in the preceding article.[1]

COMMENT

Interpretation of the results of this study must be made with due consideration for the method used in assessing osseous growth. The question might be raised as to whether it is legitimate to use standards derived from the more favored socioeconomic group of the University of Chicago Laboratory Schools to assess the progress of children in an institution. The answer, according to Todd, would be "yes," because the standard represents a relatively stable group and therefore suitable for purposes of comparison. All dietary groups of the present study were retarded by more than 10 per cent, according to these standards. Even if it is assumed that, owing to heredity, this is a normal variable for these children, it is still a fair standard to use in comparing the progress of the three dietary groups, since the same standard is applied to all and since it is relative rather than actual gain that is important. It seems probable, however, that the Carter norms represent more nearly standards which should be attained on the average by well nourished children and that the negative deviations of the children of this study represent nutritional retardation. This is indicated by the fact that the children receiving only 1 pint (473 cc.) of milk supplement decreased their deficits in ossification ratios by an amount equivalent to approximately one third of a year's growth.

Most writers on this subject of anatomic age have appeared to ignore the nutritional factor save as it is accounted for in socioeconomic status. Todd,[13] however, described four markedly different series of norms

13. Todd, T. W.: Human Bodies and Human Beings, Sigma Xi Quart. **21**:123, 1933.

which he obtained from (1) bodies of children who had died of various causes, (2) children in a low economic group, (3) average public school children and (4) winners in a school health contest; he indicated that the differences may be in part attributed to nutrition. The present study is the first to demonstrate experimentally by this method the effect nutrition may have on rate of osseous development in children from 4 to 15 years of age.

The lack of any significant difference between the group receiving plain evaporated milk and the group receiving irradiated evaporated milk may have several explanations. In the first place, the children may have been previously obtaining enough vitamin D for their needs. The home was in the country, and the children were out of doors most of their waking hours from early spring till late fall. They may therefore have obtained sufficient vitamin D from sunshine, enough being stored to last them through the winter months. A second explanation is that the 70 units of vitamin D which the milk supplied may not have been enough to produce measurable differences under the conditions of the experiment, even though it may have had a favorable influence. Even though the groups were as well matched and all other conditions were as well controlled as possible in an experiment of this type, variables were bound to occur, which might obscure small differences due to experimental procedure. Furthermore, several other dietary constituents were supplied in much more abundant amounts by the supplement than vitamin D, notably calcium, phosphorus and vitamins A, B_1 and B_2, and some or all of these were apparently limiting factors for the growth of bone, as judged by the favorable effect of milk alone. It may be, then, that vitamin D was also needed but that larger amounts would be required to demonstrate this fact.

Of particular interest in connection with these results is the difference which the simple addition of a pint of milk made in the growth of these children. The regular institutional diet lacked a number of dietary essentials, and the milk supplied some of these. There is probably no other single addition that would have added as much in quality with a similar addition of energy value. Although the diet was not thereby made perfect, the daily addition of the constituents of a pint of milk made a considerable difference in the skeletal development in this group of children. A third of a year's growth is an appreciable amount of gain over the average to be expected from one simple addition. Even with this supplement, however, the diet was still far from optimum, especially in vitamin C. It would be of interest to know how much of their arrears in osseous development these children might have made up in a year had a fully adequate diet been provided and how nearly they would approach the standards if this optimum diet or even the milk supplement could be continued throughout the period of growth.

SUMMARY

Roentgenograms of the wrists and hands of 108 children were taken at the beginning and at the end of a calendar year, and the progress in osseous development, as indicated by changes in the Carter ossification ratio, was followed. One third of the children were kept on the institutional diet as controls; one-third were given a pint equivalent of evaporated milk, and one-third were given an equal amount of irradiated evaporated milk. The most significant comparisons are those made for 24 selected trios of children, including 1 child from each dietary group, who were matched at the beginning for sex and for stage of osseous development.

By all methods of comparison the groups given a supplement showed somewhat greater progress than did the control group; these differences all tended in the same direction and were significant. There was no significant difference between the two groups receiving milk. Though all groups at the outset were retarded in respect to the Carter norms and were still retarded at the end of the study, both the groups given a supplement reduced their deficits to a greater degree than did the control group. This is shown by the following summary:

1. The percentage of children in more favorable relation to the Carter standard for age at the end than at the beginning of the study was 17 for the control, 50 for the milk and 46 for the D milk group.

2. The mean gain in Carter points for the three groups was 6 for the control, 8.3 for the milk and 8.2 for the D milk group, an advantage of 2.3 and 2.2 points, respectively, in favor of the milk groups.

3. The control group as a whole gained 79 per cent of the expected quota; each group given a supplement gained 115 per cent of the expected amount.

4. In the matched trios the control child made the greatest annual gain in 5 (21 per cent) of the comparisons, the child given plain milk in 10½ (44 per cent) and the child given D milk in 8½ (35 per cent). The amount of the superiority is shown in a comparison of the partners in the groups as to differences in variation from expected gain, the most accurate test of the data. The mean advantage of the children in the groups receiving milk over their control partners was 2.7 points. This difference is statistically significant. In terms of growth it amounts to more than a third of a year's quota of expected gain.

5. The daily addition of the constituents of a pint of milk proved a factor of safety in a rather mediocre institutional diet.

Prof. Frank N. Freeman, of the Department of Education, made available facilities for studying the roentgenograms, and Dr. Charles D. Flory and Dr. E. C. Bolmeier, of the same department, gave help and criticism. Acknowledgment is made to the Ritter Dental Equipment Company, especially to Mr. J. M. Dickinson, for the loan of the x-ray apparatus.

SEDIMENTATION RATE IN NUTRITIONAL ANEMIA OF INFANTS AND CHILDREN

ITS RESPONSE TO TREATMENT WITH IRON (FERROUS SULFATE)

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The purpose of this paper is to report the changes in the sedimentation rate of a group of infants and children with nutritional anemia due to a deficiency in iron. It has been generally accepted that dilute suspensions of cells cause accelerated rates of sedimentation and that the speed of sedimentation is inversely proportional to the concentration or the volume of the red blood cells. The present study was undertaken to collect data and to investigate thoroughly the significance of isolated observations of untreated nutritional anemia in which the red blood cells, contrary to this theory, settled at normal rates. In the course of this study it became apparent that such a discrepancy is not uncommon and that, with certain limitations, the periodic determination of the sedimentation rate may be employed as an additional guide in the management of nutritional anemia and also as an aid in the differential diagnosis of anemia complicated by infection.

It was also possible in this study to determine the potency of small doses of ferrous sulfate as an antianemic agent. This determination was undertaken because recent reports have emphasized the greater utilization of iron from the ferrous salts.

APPARATUS AND METHODS

The investigation was facilitated by the employment of a sedimentation tube which requires capillary blood and which is therefore especially suitable for use with young children. The method previously described,[1] although it requires blood from the finger, differs from other methods requiring capillary blood in that it embodies the basic specifications and features of a standard venipuncture method. Comparative tests have already established the close approximation of readings with the two kinds of tests. The reliability and simplicity of the capillary blood method have been sufficiently demonstrated in a large experience over many years.

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Read (in part) before the Section on Pediatrics, New York Academy of Medicine, New York, Dec. 10, 1936.

1. Smith, C. H.: A Method for Determining the Sedimentation Rate and Red Cell Volume in Infants and Children with the Use of Capillary Blood, Am. J. M. Sc. **192**:73 (July) 1936.

The essential features of the test may be briefly outlined as follows: After thorough preliminary rinsing of the pipet (fig. 1 *A*) with 5 per cent solution of sodium citrate, which is used as the anticoagulant, 0.04 cc. of the solution (measured by the lower graduation on the pipet) is expelled into an ordinary test tube (fig. 1 *B*). It has been found that the sedimentation rate is not perceptibly influenced if the amount of anticoagulant employed varies between 0.04 and 0.05 cc. but that clotting may occur if less than this minimum amount is used. A free flow of blood from the finger is readily obtained with an automatic lancet. The 0.3 cc. of blood required for the test is withdrawn by three consecutive aspirations

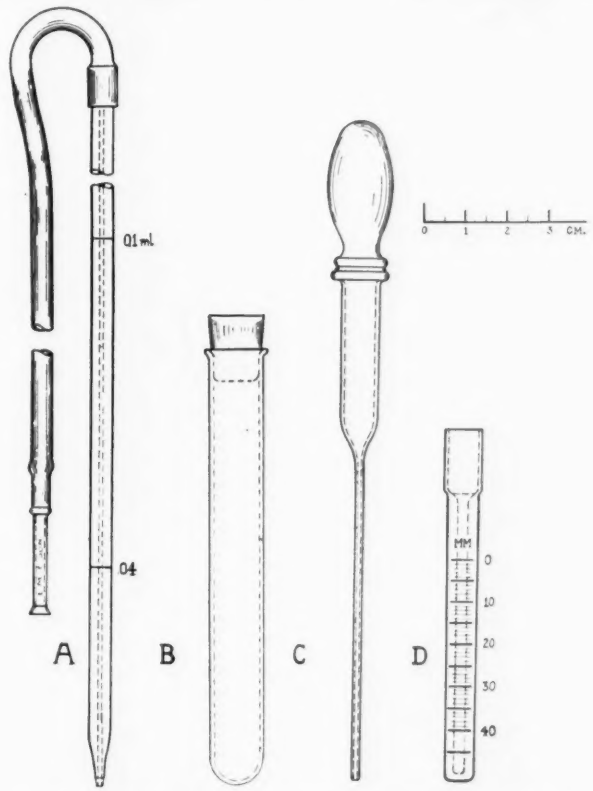

Fig. 1.—*A*, pipet for measuring the citrate solution and for collecting blood; *B*, test tube for the reception and admixture of citrate solution and blood; *C*, pipet with bulb for transferring the citrated blood to the sedimentation tube, *D*.

of 0.1 cc. each with the same pipet (fig. 1 *A*). As each fraction of blood is transferred to the test tube, it is shaken vigorously to secure thorough admixture with the sodium citrate solution. After the expulsion of the second 0.1 cc., some of the citrated blood is sucked up the length of the pipet and is returned to the test tube. After the addition of the third 0.1 cc. of blood, the tube is corked, and the contents are thoroughly admixed once more. The prevention of clotting, which is essential for accurate determinations, depends on a free flow of blood, on the employment of sufficient anticoagulant and on thorough agitation of the citrated blood while the specimen is being collected.

The citrated blood is transferred to the sedimentation tube (fig. 1 *D*) by means of a simple capillary pipet or a Wright pipet (fig. 1 *C*). The capillary portion of the pipet must be of a bore adequate to fit easily within the sedimentation tube and must be long enough to reach the bottom. The tube is filled slowly to the uppermost 0 mark. It is then placed in a rack, and the level of the upper layer of the sinking erythrocytes is recorded at the end of one hour from the millimeter graduations on the tube. Although readings in this study were made at intervals of fifteen minutes, it is obvious that for practical purposes the level at the end of one hour is entirely satisfactory as the sole measure of the rate of sedimentation.

In this investigation the hemoglobin value was determined directly in grams with Hellige tubes whose accuracy had been checked by an oxygen capacity method. Counts of red and white blood cells and smears for differential counts were made from the blood obtained by puncture of the finger. The volume of packed red blood cells, expressed as a percentage of the whole blood, was determined by the use of the sedimentation tube as a hematocrit. In this instance heparin was employed as the coagulant, since its use permits the estimation of the volume of packed cells in undiluted and unaltered blood.[2] The percentage representing the volume of packed cells was slightly lower than that obtained in the previous study,[1] since the heparinized blood was centrifugated at a rate of 4,000 revolutions per minute for one-half hour. This rate assured complete packing without injury to the cells. The hematocrit value was obtained after centrifugation by multiplying the height of the column of packed cells (in millimeters) by two.

Reticulocyte counts were made according to a modification of the technic suggested by Osgood[3] and of methods previously described, in which blood is mixed with an oxalated solution of brilliant cresyl blue. The stock solution of the stain is prepared by dissolving 1 Gm. of brilliant cresyl blue in 100 cc. of 3 per cent solution of sodium citrate. Five to 6 drops of the filtered stain (10 cc. fractions may be filtered as required and kept cold) is thoroughly mixed in a small test tube with approximately 4 drops of blood from the finger. The mixture is permitted to stand for at least half an hour, during which period it is shaken several times. A drop is spread on the slide in the manner of a blood smear and is dried in air. The smear is subsequently counterstained with Wright's stain for about ten to fifteen seconds. Water is then added and is allowed to remain for the same length of time. The slide is washed thoroughly under the cold water tap and is dried in air. At least 500 red blood cells should be counted in the determination

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2. The mixture of oxalates recommended by Heller and Paul (Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, J. Lab. & Clin. Med. **19**:777 [April] 1934) may be substituted for heparin in determining the volume of packed cells. Four hundredths cubic centimeters of the oxalate mixture (1.5 Gm. of ammonium oxalate and 1 Gm. of potassium oxalate dissolved in 100 cc. of water) is measured out with the pipet used in the sedimentation test and is expelled into a test tube, where it is allowed to dry. This serves as sufficient anticoagulant for 0.3 to 0.4 cc. of blood from the finger which is obtained with the same pipet. By means of a Wright pipet the sedimentation tube is filled to the mark 0 with the oxalated blood, and subsequent centrifugation and readings are carried out as with heparinized blood. After centrifugation at a rate of 2,500 revolutions per minute for one-half hour, the resulting hematocrit value is only 1 to 2 per cent greater than at the higher rate employed in this study.

3. Osgood, E. E., and Wilhelm, M. M.: Reticulocytes, J. Lab. & Clin. Med. **19**:1129 (July) 1934.

of the reticulocyte percentage. With this method, clotting is inhibited when the specimen of blood is brought into contact with the stain, since the latter is dissolved in citrate solution instead of in saline solution, as directed by Osgood.

From the hemoglobin content, the erythrocyte count and the hematocrit reading 2 additional values were calculated. The mean volume of the individual red blood cell, measured in cubic microns, was obtained by dividing the volume of packed cells in 1,000 cc. of blood (percentage of cells from the hematocrit times 10) by the erythrocyte count in millions per cubic millimeter. The mean hemoglobin content in the individual red blood cell, expressed in micromicrograms, was obtained by dividing the amount of hemoglobin in 1,000 cc. of blood (hemoglobin in grams times 10) by the erythrocyte count in millions per cubic millimeter. As has been pointed out by many observers, these two measurements facilitate the classification of the anemia and serve as a valuable aid during the course of treatment.

RESULTS

The results presented in this paper are based on data collected in 105 observations on 16 infants and children with anemia, ranging in age from 5 months to 6½ years. The common hematologic features in each instance consisted of diminished hemoglobin, erythrocyte and hematocrit values. In 5 cases the child had either recently recovered from an infection, or an infection was present complicating anemia during the period of observation. In general, however, the origin of the anemia could be ascribed to faulty nutrition due to dietary deficiencies; this opinion was borne out by the complete restitution of the blood elements when iron was administered.

Normal Values.—The problem of treatment involved the designation of normal values, and for the subjects included in this study this was difficult because of the changing levels of the blood elements during the period of growth. The most significant figure in evaluating the influence of anemia on the rate of sedimentation and the subsequent effect of the administration of iron is that denoting the volume of packed cells in a given specimen of blood. For a small control series of 38 determinations for a group of 24 healthy infants and children corresponding in age to the children in the group with anemia the corpuscular volume varied between 36 and 42 per cent. The values at the lower extreme were obtained for the blood of infants and the higher ones for that of older children. In a recent study of a more extensive series of cases, Mugrage and Andresen [4] found that the mean total volumes of packed cells for the various age levels corresponding to the age levels in this study varied approximately from 36 to 40 per cent. Osgood and Baker [5] recently found for 215 children aged from

4. Mugrage, E. R., and Andresen, M. I.: Values for Red Blood Cells of Average Infants and Children, Am. J. Dis. Child. **51**:775 (April) 1936.

5. Osgood, E. E., and Baker, R. L.: Erythrocyte, Hemoglobin, Cell Volume and Color, Volume and Saturation Index Standards for Normal Children of School Age, Am. J. Dis. Child. **50**:343 (Aug.) 1935.

4 to 13 years an average volume of 37 per cent, with an average of 34.5 to 36.7 per cent for children aged from 4 to 7 years (after correction for shrinkage caused by the use of oxalate as an anticoagulant).

On the basis of the foregoing data, the value of 36 per cent was regarded as the minimum normal level for the group of children under consideration in terms of which recovery from anemia was to be judged. It must be realized, however, that this figure is arbitrary, since information concerning the hematologic concentrations indicative of optimum growth of the child is still limited. Lower values may be encountered occasionally for young infants in whom adjustment to the pronounced changes of the neonatal period has not yet been completed. Also, a cell volume of 36 per cent, while it represents the average for the infant, drops gradually to the lower limits of the normal level as the child's age increases. This hematocrit value, however, was associated with at least a minimum normal content of hemoglobin and red blood cells for children of the ages under consideration. For hemoglobin, the minimum of 10 Gm. per hundred cubic centimeters of blood for the infant[6] has been found to apply to the young child as well.[5] The basic erythrocytic count approximated 4,000,000 red blood cells, with counts slightly below this level for children under 1 year of age and slightly above it for older children. The fact must be emphasized again that these figures for the cell volume, the hemoglobin content and the erythrocyte count represent borderline levels between a state of anemia and the threshold of recovery.

With the microsedimentation method described, the rate of settling of the blood of normal infants and children has been established in a previous investigation.[1] For the single determination at the end of one hour, the average was 9 mm., with a variation from 3 to 13 mm. For the purposes of classification, 13 mm. in one hour was regarded as the most rapid rate of sedimentation of normal blood.

ILLUSTRATIVE CASES

Sedimentation Rate in Cases of Uncomplicated Nutritional Anemia.—Of 16 cases in which periodic determinations of the various components of the blood and the rate of sedimentation were recorded, 5 were cases of anemia complicated by infection. The reactions to blood tests within each group were so consistent that several cases will suffice to illustrate the essential features of each.

It is obvious from the cases recorded in table 1 that normal sedimentation rates may be obtained with specimens of blood in which the hemoglobin, erythrocyte and hematocrit concentrations are reduced

6. Smith, C. H.: Management of Nutritional Anemia in Infancy, M. Clin. North America **20**:933 (Nov.) 1936.

Case No.	Patient	Age	Date	Hemoglobin: In Whole Blood, Gm. per 100 Cc.	Hemoglobin: Mean Content per Red Cell Micro-micro-grams	Red Blood Cells: Millions per Cu. Mm.	Red Blood Cells: Volume of Packed Cells per 100 Cc.	Red Blood Cells: Mean Cell Volume, Cubic Microns	Reticulated Cells, %	Sedimentation Rate, Mm. in 1 Hr.	Treatment
			1937								
1	N. D.	20 mo.	5/ 1	6.0	14.7	4.08	27	66.1	1.3	17	5/4/37, ferrous sulfate started; 8 grains daily
			5/ 6	6.0	17.6	3.40	26	76.4	1.4	15	
			5/11	8.2	20.4	4.02	36	89.5	11.7	7	
			5/15	10.0	23.2	4.31	38	88.1	4.3	3	
			5/22	11.8	26.1	4.51	40	88.6	1.1	6	
			6/ 1	12.0	28.5	4.20	42	100.0	0.5	10	
			1937								
2	P. L.	11 mo.	5/15	8.0	17.7	4.51	32	70.9	2.1	9	5/15/37, ferrous sulfate started; 8 grains daily
			5/18	8.0	18.6	4.28	32	74.7	5.2	10	
			5/20	9.0	18.7	4.80	35	72.9	5.0	6	
			5/22	9.0	20.0	4.50	36.5	81.1	3.0	9	
			5/27	11.8	26.7	4.41	40	90.7	3.5	6	
			1936								
3	W. W.	16 mo.	11/26	3.0	17.6	1.70	12	70.5	10.0	17	11/27/36 and 11/28/36, transfusions
			11/29	4.8	18.1	2.64	19	71.9	7.0	15	11/27/36, ferrous sulfate started; 12 grains daily
			12/ 4	6.4	20.6	3.11	26	83.6	26.0	10	
			12/ 8	8.4	22.7	3.69	32	86.7	12.4	6	
			12/16	11.4	26.8	4.25	40	94.1	4.0	5	
			12/29	12.6	27.2	4.62	42	90 9	1.9	4	
			1937								
			1/ 7	13.2	29.1	4.53	43	94.9	0.8	7	1/2/37, ferrous sulfate reduced to 6 grains daily
			2/ 2	13.4	28.5	4.69	41	87.4	0.5	8	2/2/37, iron therapy discontinued
			3/10	12.4	30.0	4.13	40	96.8	0.5	13	3/11/37, ferrous sulfate resumed; 12 grains daily
			3/25	13.6	30.1	4.52	39	86.2	0.8	11	
			4/ 8	13.4	30.3	4.42	40	90.4	0.9	12	
			1936								
4	D. F.	14 mo.	6/20	6.0	15.6	3.84	26	67.7	....	15	6/20/37, ferrous sulfate started; 8 grains daily
			6/25	7.4	21.2	3.48	30	86.2	....	8	6/25/37, ferrous sulfate increased to 12 grains daily
			7/ 7	11.0	23.6	4.65	39	83.8	....	5	7/7/37, ferrous sulfate, 6 grains daily
			7/28	12.2	27.3	4.46	38.5	86.3	....	7	7/28/37, iron therapy discontinued
			9/22	12.2	31.0	3.93	38	96.6	....	7	9/22/37, ferrous sulfate resumed; 6 grains daily
			11/ 5	13.0	32.1	4.05	42	103.7	....	6	11/5/36 to 11/29/36, ferrous sulfate, 8 grains daily
			12/ 3	13.6	30.0	4.53	44	97.1	....	6	
			1936								
5	C. B.	6 yr.	10/ 7	7.0	23.1	3.03	28	92.4	....	20	10/11/36, iron and ammonium citrates started; 36 grains daily
			10/14	6.5	21.7	2.99	27	90.3	....	20	10/14/36, iron and ammonium citrates increased to 48 grains daily
			10/28	9.0	29.5	3.05	32	104.9	....	8	
			10/30	9.6	27.5	3.48	32	91.9	....	8	11/4/36, iron and ammonium citrates increased to 90 grains daily
			11/ 5	10.0	28.2	3.54	34	96.0	....	8	
			11/ 7	10.0	27.9	3.58	35	97.7	....	4	
			11/14	12.0	29.1	4.11	40	97.3	....	4	
			11/17	12.0	29.3	4.09	40	97.7	....	5	11/17/36, iron and ammonium citrates, 45 grains daily
			11/23	12.8	26.7	4.79	41	85.5	....	6	12/15/36, iron therapy discontinued
			1937								
			2/ 4	14.6	33.0	4.42	42	95.0	....	7	

below normal levels. In case 2, for instance, rates of 9, 10 and 6 mm. in one hour were observed, associated with respective hematocrit values of 32, 32 and 35 per cent. In case 3 the rates of 10 and 6 mm. were associated with hematocrit values of 26 and 32 per cent, respectively, and in case 4 a rate of 8 mm. was associated with a hematocrit reading of 30 per cent. In case 5 the red blood cells settled to 8 mm. with hematocrit values of both 32 and 34 per cent, and with a rise in the latter to only 35 per cent, the sedimentation rate dropped to 4 mm. or one-half the original rate. Again, with 13 mm. in one hour as the most rapid sedimentation rate occurring normally, rates slightly above this figure were noted with hematocrit values much below normal. In case 1, for instance, with the volume of packed cells at 27 and 26 per cent, rates of 17 and 15 mm., respectively, were obtained.

In severe anemia, when there is a pronounced reduction in the hematocrit value, the line of demarcation between the plasma and the sedimented cells is not always distinct. This haze, or *unscharfen Zone*,[7] interferes with an exact reading of the height of the sedimentation column. In case 3 it was noted that with hematocrit readings of 12 and 19 per cent the respective sedimentation rates of 17 and 15 mm. were only approximate. To check the accuracy of these determinations, parallel tests were carried out with venous blood by the Cutler method. The uppermost level of this zone was exactly the same with the two methods. In all other determinations, however, with a moderately decreased range of hematocrit values (26 per cent or above), the packing was firm, as visualized with a magnifying lens.

Again, while appreciable slowing of the sedimentation rate occurred with rising hematocrit values, a high degree of correlation was not always apparent. In case 1, rates of 7 and 3 mm. in one hour were noted in association with respective hematocrit readings of both 36 and 38 per cent; in case 2, 9 mm. of settling occurred in association with readings of both 32 and 36.5 per cent; in case 3, rates of 6 and 4 mm. were associated with respective hematocrit values of 32 and 42 per cent. In case 5, red blood cells sedimented more rapidly with a hematocrit value of 42 per cent than with one of 35 per cent (7 mm. of settling in the former as compared with 4 mm. in the latter).

With the elevation in hemoglobin, erythrocyte and hematocrit values during the administration of iron, the measurements derived from these determinations revealed corresponding fluctuations. In this study a mean hemoglobin content per red blood cell of approximately 23 micromicrograms was usually associated with definite regeneration of the blood elements. During the period of recovery, however, before the minimum levels have been attained, the concentration of hemoglobin in

7. Reichel, H.: Blütkörperchensenkung, Berlin, Julius Springer, 1936.

the individual red blood cell may be normal or increased. In case 5 (table 1), for instance, it was observed that concentrations of 29.5, 27.5, 28.2 and 27.9 micromicrograms were found in the presence of subnormal hemoglobin and erythrocyte values for whole blood. With few exceptions, the cases in this study also bore out the observation of Guest and Brown,[8] who found that a hemoglobin content of 20 micromicrograms or less per cell justifies a diagnosis of anemia. That a normal sinking velocity of the red blood cells may be found in anemia is further demonstrated by the instances of reduced concentrations of hemoglobin per red blood cell in cases 1 to 3 (table 1) with accompanying normal rates of sedimentation.

It was also observed that when the mean volume of the single cell rose to approximately 82 cubic microns, definite recovery was in progress. With continued iron therapy this value was soon exceeded. In case 2 (table 1) the first 4 determinations revealed individual cell volumes of less than this value, yet the sedimentation rates were normal. In general, the lack of correlation between the sedimentation rate, on the one hand, and the mean size and hemoglobin concentration of the single red blood cell, on the other, occurred most often before treatment and during the early part of the period during which iron was administered.

Sedimentation Rate in Nutritional Anemia Complicated by Infection.—The data summarized in table 2 reflect the sedimentation reactions of the blood in infections of varying grades of severity, although no infection was so acute as to preclude the successful administration of iron. While infection undoubtedly contributed to the causation of the anemia in these instances, an underlying nutritional defect was also present in cases 7 and 8. In both of these the diet had consisted almost exclusively of milk; and in addition 1 patient (case 8) was a Negro infant, 1 of premature twins. The determinations presented in the latter case were selected from more extensive data in order to illustrate the response of the blood when recurrent infections occur in a particularly susceptible infant.

In every case an increased rate of sedimentation persisted for the duration of the illness and remained slightly elevated during the final stage of the subsiding infection. In the latter phase, as exemplified by case 7, it constituted a more sensitive indicator of residual infection than did the leukocyte or the differential count.

It will be observed in every case that during the period of infection when the sedimentation rate was still elevated, the administration of

8. Guest, G. M., and Brown, E. W.: Erythrocytes and Hemoglobin of the Blood in Infancy and in Childhood: I. Size and Hemoglobin Content of Erythrocytes in Nutritional Anemia, Am. J. Dis. Child. **52**:616 (Sept.) 1936.

iron was effective in stimulating the regeneration of hemoglobin and of red blood cells. While normal levels were reached in cases 6 and 7, the results in case 8 were less satisfactory. The minimum levels of recovery obtained with treatment for the child in case 8 and his brother probably represented the diminished regenerative capacities for hemapoiesis during the course of continued infection. It is noteworthy,

TABLE 2.—*Examples of Changes in the Sedimentation Rate in Cases of Nutritional Anemia Complicated by Infection*

	Hemoglobin		Red Blood Cells					
Date	In Whole Blood, Gm. per 100 Cc.	Mean Content per Red Cell, Micro-micro-grams	Millions per Cu. Mm.	Volume of Packed Cells, Cc. per 100 Cc.	Mean Cell Volume, Cubic Microns	Reticulated Cells, %	White Blood Cells per Cu. Mm.	Sedimentation Rate, Mm. in 1 Hr.
Case 6: J. D., aged 3 years; follicular tonsillitis								
1935								
12/27	9.0	19.6	4.59	30	65.4	...	8,200	27
12/30	Iron and ammonium citrates, 45 grains daily							
1936								
1/ 5	9.0	18.7	4.79	33	68.9	...	21,200	28
1/10	Iron and ammonium citrates, 90 grains daily							
1/14	10.0	19.4	5.15	38	73.8	...	22,000	24
1/15	10.4	22.1	4.71	36	76.4	...	27,400	25
1/23	11.4	21.5	5.28	41	77.6	...	8,500	15
1/25	12.0	25.3	4.73	40	84.6	...	11,300	12
1/16 1/20 1/25	Intramuscular injections of liver extract							
Case 7: M. T., aged 19 months; subacute purulent otitis media								
1937								
5/29	7.0	20.1	3.49	30	85.9	4.5	9,900	29
5/29	Ferrous sulfate, 8 grains daily							
6/ 1	7.8	21.6	3.60	33	91.6	2.0	15,700	30
6/ 8	10.0	22.5	4.43	37	83.5	8.6	13,400	20
6/12	11.2	25.4	4.40	40	90.9	3.7	10,000	19
6/19	12.8	29.9	4.27	43	100.7	2.0	8,400	12
6/24	12.8	27.8	4.60	42	91.3	1.8	12,000	9
7/ 1	12.8	29.8	4.32	42	97.2	1.5	7,600	8
Case 8: A. W., aged 15 months; recurrent respiratory infections								
1936								
10/22	4.3	....	2.30	..	....	...	6,500	..
10/22 to 11/12, iron and ammonium citrates, 24 to 48 grains daily								
11/19	4.8	20.1	2.39	21	87.8	2.0	12,800	26
11/19	Ferrous sulfate, 12 grains daily							
11/25	7.0	23.2	3.01	28	93.0	7.0	32,400	19
11/25	Ferrous sulfate, 18 grains daily							
12/ 5	9.0	22.6	3.97	34	85.6	3.0	11,600	9
12/15	10.0	23.1	4.32	36	83.3	1.4	13,200	14
1937								
1/ 5	10.0	23.1	4.33	35	80.8	1.7	17,800	23
2/18	10.0	22.8	4.38	36	82.1	1.0	21,300	12

however, that the retardation of the sedimentation rate observed in cases of uncomplicated anemia (table 1) is also manifest in this instance (case 8) with active infection present. On November 25, six days after the administration of an effective dose of iron with a hematocrit value of 28 per cent and a leukocyte count as high as 32,400, the sedimentation rate was only 19 mm., and on December 5 a normal sedimentation rate of 9 mm. was recorded, with a hematocrit value of only 34 per cent.

In general, however, the cases reported in table 2 reveal that the sedimentation rate remained elevated during the period of infection despite pronounced increments in the various constituents of the blood. To what extent the speed of settling was influenced by the specific retarding effect of regenerating blood in the type of case under consideration cannot be definitely stated.

The Relation Between the Volume of Packed Red Blood Cells and the Sedimentation Rate During Various Phases of Nutritional Anemia.—In this study 36 determinations were made for 14 children with hematocrit values below 36 per cent, the lower limit of the normal value. The distribution of sedimentation rates for this group is shown in figure

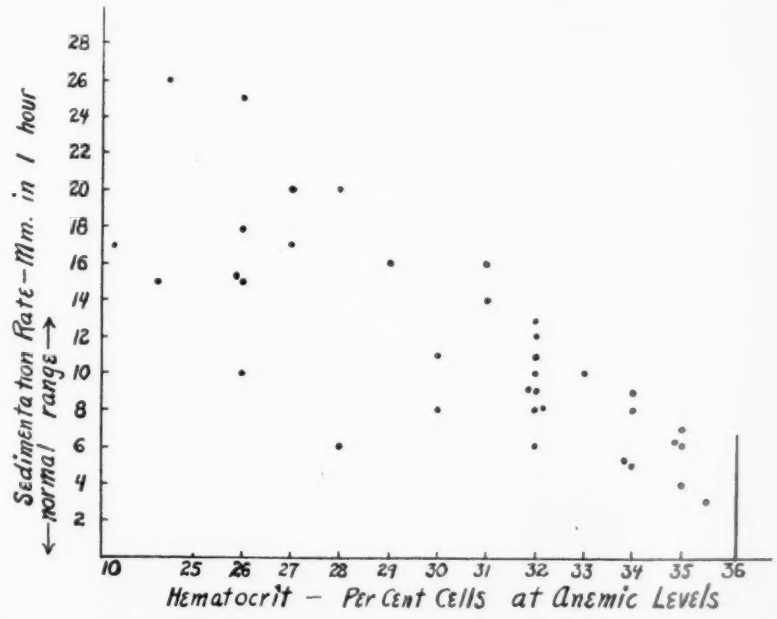

Fig. 2.—The distribution of sedimentation rates in relation to hematocrit values at various levels of anemia. The cell volumes below 36 per cent correspond to the levels of anemia.

2. In 23 determinations, or approximately 65 per cent, the red blood cells settled at normal rates. It will be noted in this chart (fig. 2) that in 6 of the remaining cases the rates were only slightly elevated, ranging from 14 to 16 mm. in one hour for children with hematocrit values varying between 19 and 31 per cent. The variability of sedimentation rates and the inherent differences existing in specimens of blood was illustrated in 4 cases of uncomplicated nutritional anemia in which the volume of packed cells in each instance was 26 per cent, but in which the red blood cells sedimented at speeds of 10, 15, 18 and 25

mm., respectively, in one hour. In general, however, the slowing of the sedimentation rate occurred with increasing volume of packed cells. It will be noted from the chart (fig. 2) that the majority of the normal sedimentation rates were obtained for children with hematocrit values ranging between 32 and 36 per cent.

In table 3 average sedimentation rates are presented in relation to hematocrit values which had reached normal levels. Although the observations are limited in number, it may be noted in this table that in almost every instance the red blood cells settled more slowly at their respective hematocrit values in the blood of the children originally anemic than in the blood of the normal children. The average of 6.77 mm. for all the observations for the anemic children in one hour, as

TABLE 3.—*Average Sedimentation Rates in Relation to the Volume of Packed Cells in the Group Originally Anemic as Compared with the Normal Group**

Volume of Packed Cells, Cc. per 100 Cc.	Group of Fourteen Originally Anemic Children		Group of Twenty-Four Normal Children	
	Average Sedimentation Rate, Mm. in 1 Hour	Number of Observations	Average Sedimentation Rate, Mm. in 1 Hour	Number of Observations
36	8.4	9	10.6	3
37	6.5	2	6.5	2
38	4.3	3	9.5	14
39	7.6	3	9.5	2
40	7.0	14	8.8	11
41	6.0	3	8.5	2
42	6.7	8	9.3	3
43	5.2	6	9.0	1
44	6.0	1		
Average	6.77		9.15	
Total		49		38

* The ages of the children in both groups ranged between 5 months and 7 years.

compared with the average of 9.15 mm. for the normal children, suggests that the particular factors which retard the rate of sedimentation at subnormal hematocrit levels continue to exert their influence during the period of recovery.

The Mean Volume of the Red Blood Cells and the Sedimentation Rate.—Fahraeus [9] pointed out that differences in the size of the red blood cell produce no significant effect on the sedimentation rate, although the size of the rouleaux and of the aggregates which they form constitute the factor of primary importance in this phenomenon. Table 4 was prepared in order to determine whether in children with nutritional anemia any relation exists between the size of the red blood cell, measured by the mean cell volume, and the speed of sedimentation.

9. Fahraeus, R.: The Suspension Stability of the Blood, Physiol. Rev. **9**:241 (April) 1929.

It is obvious from the findings recorded in this table that the sinking velocity of the red blood cell is not dependent on its size and that comparable sedimentation rates are associated with considerable differences in the volume of the individual red blood cell.

Response of the Hematologic Factors and of the Sedimentation Rate to Ferrous Sulfate Therapy.—The treatment which was required to follow the changes in the sedimentation reaction during recovery from anemia presented an opportunity of testing the efficacy of ferrous sulfate. Recent claims for the superiority of this over the ferric compounds have been based on the experimental evidence that ferrous salts are more readily absorbed from the gastrointestinal tract of animals and on clinical experience demonstrating that a cure may be effected with smaller doses of the drug. The latter consideration is particularly attractive when iron compounds are to be prescribed for young children. Ferrous sulfate was administered in the form of a solution, each teaspoonful containing 2 grains (0.13 Gm.) of this salt, or approximately 26 mg. of metallic iron.[10]

TABLE 4.—*Average Sedimentation Rates in Relation to the Mean Volume of the Red Cells in the Group of Anemic Children*

Mean Red Cell Volume, Cubic Microns	Average Sedimentation Rate, Mm. in 1 Hour	Range of Sedimentation Rates, Mm. in 1 Hour	Number of Observations
60-65	5.50	5-6	2
65-70	14.25	7-18	4
70-75	9.30	3-17	10
75-80	8.60	3-16	10
80-85	9.70	4-25	11
85-90	7.77	3-26	18
90-95	8.50	2-20	13
95-100	6.90	4-13	9
100-105	7.60	2-12	5
105-110	12.50	11-14	2

Of the 16 children studied, 10 were treated with ferrous sulfate, 5 with iron and ammonium citrates, and 1 with a combination of the two. Examinations of the blood in 13 cases were made within sufficiently short intervals to permit the appraisal of fluctuations of the individual condition of the blood. The results of these are summarized in table 5. The average gain in hemoglobin per day obtained with the ferrous salt was 0.199 Gm. as contrasted with a gain of 0.127 Gm. obtained with the ferric salt. The results with iron and ammonium citrates noted in this table correspond to those usually obtained with its use and confirm its effectiveness when administered in sufficient doses. For iron and ammonium citrates the dose that has been suggested for the infant is 1 grain (0.06 Gm.) per pound of body weight, or a total of 15 to 30

10. The preparation employed was furnished by Smith, Kline & French, Philadelphia.

TABLE 5.—*Summary of Results with Iron Salts, Including Their Effect on the Sedimentation Rate*

Case No.	Patient	Age	Iron Salt	Daily Dose, Grains	Hemoglobin, Gm. per 100 Cc.		Red Blood Cells				Reticulocyte Peak		No. of Days Treated	Total Hemoglobin Gain Under Treatment, Gm.	Hemoglobin Gain per Day, Gm.	Sedimentation Rate, Mm. in 1 Hour		Comment
							Millions per Cubic Mm.		Volume of Packed Cells, Cc. per 100 Cc.		Percentage	Days After Start of Treatment						
					Initial	Final	Initial	Final	Initial	Final						Initial	Final	
1	R. H.	7 mo.	Ferrous sulfate	8	6.8	11.0	3.75	4.56	26	40	9.4	6	29	4.2	0.145	18	11	
2	N. D.	20 mo.	Ferrous sulfate	8	6.0	12.0	3.40	4.20	26	42	11.7	7	28	6.0	0.214	15	10	Same as case 1, table 1
3	P. L.	11 mo.	Ferrous sulfate	8	8.0	11.8	4.51	4.41	32	40	5.2	3	12	3.8	0.317	9	6	Same as case 2, table 1
4	A. W.	15 mo.	Ferrous sulfate	12-18	4.8	10.0	2.39	4.32	21	36	7.0	6	26*	5.2	0.200	26	14	Same as case 8, table 2; maximum response noted in 26 days (12/15/36)
5	M. W.	15 mo.	Ferrous sulfate	12-18	5.4	10.0	3.11	4.54	26	36	7.7	9	26	4.6	0.176	25	10	Twin of patient in case 4
6	J. J.	5 mo.	Ferrous sulfate	6	9.0	13.8	4.46	4.94	28	41	...	..	54	4.8	0.089	6	4	
7	D. F.	14 mo.	Ferrous sulfate	6-12	6.0	12.2	3.84	4.46	26	38.5	...	..	38	6.2	0.163	15	7	Same as case 4, table 1; maximum response as of 7/28/36
8	W. W.	16 mo.	Ferrous sulfate	12	4.8	13.2	2.64	4.53	19	43	26.0	7	41	8.4	0.205	15	7	Same as case 3, table 1; maximum response noted in 39 days (1/7/36)
9	M. T.	19 mo.	Ferrous sulfate	8	7.0	12.8	3.49	4.27	30	43	8.6	10	21*	5.8	0.276	29	12	Same as case 7, table 2; maximum response noted in 21 days (6/19/37)
10	R. S.	25 mo.	Ferrous sulfate	8	8.4	13.0	4.09	4.84	33	43	5.5	7	23	4.6	0.200	10	3	
11	J. R.	22 mo.	Iron and ammonium citrates	22	8.5	13.0	4.43	5.16	34	40	...	..	34	4.5	0.132	5	5	
12	J. D.	3 yr.	Iron and ammonium citrates	45-90	9.0	12.0	4.59	4.73	30	40	...	..	26*	3.0	0.115	27	12	Same as case 6, table 2
13	C. B.	6 yr.	Iron and ammonium citrates	36-90	7.0	12.8	3.03	4.79	28	41	...	..	43	5.8	0.135	20	6	Same as case 5, table 1

* Cases of nutritional anemia complicated by infection.

grains (0.97 to 1.94 Gm.) per day.[6] Ferrous sulfate was well tolerated, and in the short experience covered by this investigation, the average daily dose required varied between 6 and 18 grains (0.34 and 1.16 Gm.) with 8 grains (0.52 Gm.) as the amount usually effective. The smaller dose of the ferrous salt also possesses the advantage of minimizing the likelihood of gastrointestinal disturbances, which are so frequently associated with the administration of iron.

The potency of the ferrous salt was reflected in the reticulocyte response in the 8 cases in which this was determined. The rise in case 8 (table 5) to 26 per cent may be related to the hemoglobin value of only 4.8 Gm. at the institution of iron therapy, which is in accord with the principle that the extent of the increase of reticulocytes is inversely proportional to the initial hemoglobin content. In this case the unusually high reticulocyte count may be attributed partly to the transfusions which were given before iron was administered. The lower reticulocyte count in case 4, with the same hemoglobin value at the start, was probably due to the depressing influence of the intercurrent infection.

Except in 1 instance (case 10, table 5) the slowest sedimentation rate did not coincide with the highest reticulocyte count. This relation was not to be expected, since the magnitude of the reticulocyte response is indicative of the degree of stimulation of the bone marrow and of the corresponding regeneration of hemoglobin and red blood cells. The measurement of the sedimentation rate, on the other hand, is influenced not alone by changes in the concentration of red blood cells but by alterations in the plasma as well.

Concurrent with the striking gains in hemoglobin and in the volume of packed red blood cells the slowing of the sedimentation rate was also noted. In cases 2, 3 and 6, however, the differences between the initial and the final sedimentation rate were less pronounced than those between respective volumes of packed cells. In case 11 the rates were identical despite an appreciable increment in the volume of red blood cells. Although the intermediary stages of recovery have been omitted from this table, it will be noted from the data that for given volumes of packed cells the sedimentation rates showed considerable variation.

COMMENT

Since the sedimentation rate is employed primarily as a means of estimating the degree of existing infection and of damage to the tissues, numerous methods have been devised to correct for the concentration of red blood cells, which, of itself, also exerts a profound influence on the sedimentation rate. This consideration derives its importance from the inverse relation which exists between the number and volume of the red blood cells and the speed of sedimentation. The devices for correc-

tion usually take the form of charts which are constructed from preliminary determinations of the sedimentation rate of varying dilutions of the red blood cells suspended in their own plasma.

The results of the present investigation, however, have shown that the red blood cells of a group of infants and children with nutritional anemia did not sink with the velocity expected from experiments with dilution. Fahraeus [9] was one of the first to point out that the degree of parallelism expected from dilution experiments (in vitro) does not regularly occur clinically. Reichel [7] more recently presented many examples of uncomplicated secondary anemia in which the sedimentation rate was normal and emphasized the lack of correlation between the two. In a study of experimental anemia in rabbits, produced by bleeding, Gregg [11] observed that in some phases of the disease the blood sedimented slowly; in acute anemia, for instance, the sedimentation rate of whole blood was accelerated, whereas in chronic anemia there was a gradual slowing of the rate both in the whole blood and in suspensions of cells in plasma. Normal sedimentation rates with low blood counts occasionally have been pointed out in the literature in case reports of various pathologic conditions. The tendency for overcorrection when the anemia is severe, as has been pointed out by Britton,[12] may also be noted in an analysis of various surveys concerned with the sedimentation rate and can be attributed only to the normal or slightly accelerated rates before correction.

The results described in this study do not conflict with the current view that, in general, dilute suspensions of erythrocytes sediment more rapidly than when the content of cells is higher. They do, however, demonstrate that the correlation between these two factors does not apply to the group of cases of nutritional anemia under consideration. The most significant observation brought to light by this investigation is that anemic blood in nutritional anemia does not behave as does diluted normal blood with regard to the sedimentation rate and that the statement frequently made that anemia is productive of accelerated sedimentation cannot be accepted without reservation.

While this study was directed toward an analysis of cases of nutritional anemia, there were other blood dyscrasias in which the sedimentation rate was (unexpectedly) normal or slightly increased despite reduced blood counts and cell volumes. In a case of erythroblastic anemia of the Cooley type, for instance, blood with a hematocrit value of 26 per cent sedimented at the rate of only 15 mm. in one hour, and

11. Gregg, R. O.: The Sedimentation Rate in Experimental Anemia (Rabbit), J. Lab. & Clin. Med. **22**:786 (May) 1937.

12. Britton, C. J. C.: The Sedimentation Rate of the Blood Findings and Interpretations in Eight Hundred Cases, New Zealand M. J. **35**:310 (Oct.) 1936.

blood with a hematocrit value of 30 per cent sedimented at the rate of 9 mm. In general, however, the results were not as consistent as in cases of uncomplicated nutritional anemia. In a case of lymphatic leukemia, with a hematocrit value of 28 per cent, the rate was 35 mm. in one hour. Reichel [7] stated that in untreated pernicious anemia the sedimentation rate is always noticeably accelerated.

The explanation for normal rates of sedimentation in anemic blood must be sought in the mechanisms ordinarily involved in the sinking of the red blood cells in plasma. The physical phenomenon of sedimentation rests ultimately on the physiologic process of the formation of rouleaux. Changes in the sedimentation rate, or in the suspension stability of the blood which it measures, may be traced to alterations in the degree of rouleaux formation and in the size of the aggregations which they form. According to Fahraeus,[9] these physical changes are brought about by the interaction between certain properties of the plasma, such as the fibrinogen and globulin content, and by the properties of red blood cells, such as their surface tension, their electrical charge and the layer of absorbed water by which they are surrounded. The failure of the red blood cells to settle out as rapidly as anticipated, finally, in the specimens of anemic blood, must be accounted for by the activity of forces peculiar to anemia which influence the formation of rouleaux. Fahraeus [9] suggested the existence of a factor counteracting the rapid sedimentation in anemia, which is related in some way to the fact that red blood cells in dilute corpuscular suspensions show a diminished tendency to collect. As has been pointed out, in the specimens with hematocrit readings as low as 12 and 19 per cent (case 3, table 1) the extent of rouleaux formation and aggregation was obviously reduced. This was manifested by the presence of a reddish haze, instead of a sharp line of demarcation, at the junction of the upper level of the column of cells and the supernatant layer of plasma. Careful examination of specimens, however, from the children with less severe anemia (having hematocrit values of 26 per cent or above) revealed no evidence of a haze, and the line between the red blood cells and the plasma was sharp. Whether the changes in the lipid content of the plasma and of the red blood cells in the small group of cases of hypochromic anemia recently reported [13] represent factors of sufficient significance to affect the sedimentation remains a matter of speculation.

Abundant experimental proof is available for the view that the controlling factors which influence the sedimentation rate reside in the

13. Erickson, B. N.; Williams, H. H.; Hummel, F. C.; Lee, P., and Macy, I. G.: The Lipid and Mineral Distribution of the Serum and Erythrocytes in the Hemolytic and Hypochromic Anemias of Childhood, J. Biol. Chem. **118**:569 (May) 1937.

plasma. Observations have been made, however, which show that the red blood cells perform more than the secondary function of contributing to changes in the rate solely through their volume. Zozaya [14] has recently pointed out that, contrary to the usual results obtained with this type of experiment, erythrocytes from different sources suspended in samples of the same plasma may sediment at widely divergent rates. It is conceivable that the normal sedimentation rates reported in this study represent the effect of alterations not alone in the plasma but in the structure of the red blood cell as well. Investigations now in progress already indicate that during the stage of response to iron therapy the erythrocyte undergoes qualitative changes, as manifested by an increased capacity for the absorption of methylene blue.

Comprehensive diagnostic inferences cannot be drawn from these studies, since the group investigated was small and the other dyscrasias of the blood, particularly those which occur in older children, await more thorough analysis. It may be restated, however, that the correlation between the speed of sedimentation and the concentration of erythrocytes, for which there is overwhelming evidence, does not apply in the cases of nutritional anemia that were studied. In this type of anemia and in the age group under consideration, normal rates of sedimentation were observed at times prior to the institution of therapy and usually occurred early in the period of recovery, when the anemia was uncomplicated. When infection supervened, however, the increased sedimentation rate was further accelerated by the added influence of a lowered cell count. With the reservations imposed by the limited data and pending modification by large series of observations, a possible deduction from the interaction of these two factors may be expressed as follows: When iron in adequate doses is administered to a young child with anemia of moderate severity, the persistence of a rapid rate of sedimentation suggests either the continued activity of an infectious process or that the diagnosis of anemia on a purely nutritional basis is to be questioned.

From these studies, it appears that the changing rate of sedimentation of the erythrocytes in cases of uncomplicated nutritional anemia during treatment constitutes a composite reaction of the various hematologic factors that enter into the phase of recovery. Finally, it is possible that more extensive observations will justify the use of the sedimentation rate as another criterion by which the effectiveness of iron therapy may be estimated.

SUMMARY AND CONCLUSIONS

A study comprising 105 periodic observations of the rate of sedimentation of the erythrocyte was made, together with observations of

14. Zozaya, J.: Factors Influencing Sedimentation Rate of Erythrocytes, Proc. Soc. Exper. Biol. & Med. **36**:182, 1937.

other hematologic factors, in 16 cases of nutritional anemia in infants and children.

The sedimentation test was performed with blood from the finger, and the results of the test closely approximated those of tests performed with venous blood. With the use of heparin or of a mixture of oxalates the sedimentation tube served also as an accurate hematocrit. Reticulocytes were stained according to a simplified method which did not require the use of previously prepared slides.

The results revealed that the red blood cells in this group of cases did not sediment with the velocity usually ascribed to diluted blood. Normal and slow rates of sedimentation were recorded in many instances prior to treatment and during the early stages of recovery.

Of 36 determinations for 14 children with hematocrit values below 36 per cent the lower limit of normal, the erythrocytes in 23, or approximately 65 per cent, settled at normal rates, and in 6 of the remaining instances the rates were only slightly elevated.

In 11 cases of uncomplicated nutritional anemia in which normal or slightly accelerated rates were noted prior to treatment, further retardation occurred with the administration of iron. On the other hand, in the 5 remaining cases in which infections of varying grades of severity complicated the anemia, elevation of the sedimentation rate persisted after treatment in spite of the regeneration of hemoglobin and of red blood cells.

After the attainment of normal levels the red blood cells settled more slowly for their respective hematocrit values in the cases of children originally anemic than for a group of normal children. The average sedimentation rate of 6.77 mm. in one hour for all observations for the group of anemic children, as compared with a rate of 9.15 mm. in one hour for the group of normal children, suggests that the factors which retard the rate at subnormal hematocrit levels continue to exert their influence during the period of recovery.

Of the 16 children, 10 were treated with ferrous sulfate, 5 with iron and ammonium citrates and 1 with a combination of the two. Smaller doses of the ferrous than of the ferric salt were required to produce a satisfactory response in the hematologic values and a retardation of the sedimentation rate.

The statement frequently made that anemia is productive of an accelerated rate of sedimentation cannot be accepted without reservation. The explanation of the normal and slow rates of sedimentation in nutritional anemia probably involves the presence of inherent factors in this condition which counteract the tendency for the rapid rates obtained with diluted normal blood and which are also noted in pathologic conditions associated with anemia.

The fluctuation in the speed of sedimentation of the erythrocytes in cases of uncomplicated nutritional amenia during treatment represents a composite reaction of the various hematologic factors comprising the process of recovery. The sedimentation rate may therefore constitute an additional clinical aid by which the effectiveness of iron therapy may be estimated.

119 East Eighty-Fourth Street.

ERYTHROCYTES AND HEMOGLOBIN OF THE BLOOD IN INFANCY AND IN CHILDHOOD

II. VARIABILITY IN NUMBER, SIZE AND HEMOGLOBIN CONTENT OF THE ERYTHROCYTES DURING THE FIRST FIVE YEARS OF LIFE

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CINCINNATI

The studies of the size and hemoglobin content of red blood cells which have been made by many investigators in recent years have yielded much valuable information concerning the normal physiology of the blood cells and their changes in different types of anemia.[1] While such studies have been concerned for the most part with adult subjects, those dealing with infants and children, although less extensive, have shown clearly that in both normal and anemic infants the red cells undergo remarkable changes during the early years of life. The literature of this phase of the subject has been adequately reviewed in this journal by Osgood and Baker,[2] Mugrage and Andresen[3] and Guest and Brown.[4]

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati.

1. Haden, R. L.: Methods and Clinical Value of the Determination of the Size of the Red Blood Cell, Am. J. M. Sc. **181**:597 (May) 1931; Red Blood Cell of Man, Internat. Clin. **1**:68 (March) 1935. Wintrobe, M. M.: Size and Hemoglobin Content of the Erythrocytes: Methods of Determination and Clinical Application, J. Lab. & Clin. Med. **17**:899 (June) 1932; Anemia: Classification and Treatment on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Corpuscles, Arch. Int. Med. **54**:256 (Aug.) 1934. Osgood, E. E., and Haskins, H. D.: Causes, Classification and Differential Diagnosis of Anemias, Based on the Detailed Examination of Over Two Hundred Patients and a Study of the Literature, Ann. Int. Med. **5**:1367 (May) 1932.

2. Osgood, E. E., and Baker, R. L.: Erythrocyte, Hemoglobin, Cell Volume and Color, Volume and Saturation Index Standards for Normal Children of School Age, Am. J. Dis. Child. **50**:343 (Aug.) 1935.

3. Mugrage, E. R., and Andresen, M. I.: Values for Red Blood Cells of Average Infants and Children, Am. J. Dis. Child. **51**:775 (April) 1936.

4. Guest, G. M., and Brown, E. W.: Erythrocytes and Hemoglobin of the Blood in Infancy and in Childhood: I. Size and Hemoglobin Content of the Erythrocytes in Nutrition Anemia, Am. J. Dis. Child. **52**:616 (Sept.) 1936.

A few examples of data obtained on samples of blood from normal and from anemic infants were presented in the first paper of this series.[4] These examples were selected to demonstrate the changes in size and hemoglobin content of red blood cells which occur with nutritional anemia: the marked microcytosis and hypochromia of the erythrocytes found in infants with severe anemia of this type, and the wide range of intermediate values for these characteristics of the erythrocytes found in milder, borderline involvement. For the proper evaluation of such observations there is needed, of course, a more fundamental knowledge than now exists of various influences which can affect the development of the red blood cells in infants. Even when such knowledge is available, however, the evaluation of findings in the blood in individual cases demands first of all the recognition of the degree of variability that may be found in red cells of blood taken from large groups of infants and children who differ in age and condition. As an approach to the problem of variability per se, this paper presents data on 615 infants and children ranging in age from birth to 5¼ years. These findings are presented in scatter charts and histograms, the principal purpose being to demonstrate the direction and magnitude of the cellular changes which may be expected at different times during this age period. More complete statistical analysis of the numerical data from which the charts were prepared will be presented in later communications.

The investigations summarized in this series of papers were begun in 1930 as a corollary to certain chemical studies of the blood cells, which are still being carried on. In those studies, values for size and hemoglobin content of the red cells were determined as helpful measures of control in the evaluation of changes in various constituents of the cells found in different pathologic conditions. Thus, part of the data included in this report were derived from samples of blood which were examined for reasons other than the objectives of the studies presented here. To amplify those observations, and to study also the variability in size and hemoglobin content of the erythrocytes as a problem in itself, a large number of samples of blood were collected more or less at random from various groups of infants. Some of these infants have been followed closely from birth, with examinations of the blood repeated at varying intervals; records of 2 such cases were presented in charts 1 and 2 of the previous paper,[4] and others will appear in later papers.

CLINICAL MATERIAL

Some subjects whose blood has been studied in the manner described were patients of the inpatient and outpatient departments of the Cincinnati Children's Hospital, of the pediatric and obstetric services of

the Cincinnati General Hospital or of the Maple Knoll Hospital; some were inmates of the St. Joseph's Infant Asylum or of the Catherine Booth Home of the Salvation Army, and others were well infants from the families of physicians or from their private practice. The last-named group of well infants is referred to (charts 11 and 13) as an optimum group merely because they came from families of higher economic levels, were reared under favorable circumstances and had been relatively free from nutritional disturbances and acute infectious diseases.

The infants were white; their parents were of widely mixed nationalities. Similar studies of Negroes were made, but they are not included in this report. This summary includes data on infants with acute infections of varying severity, but it excludes those with primary dyscrasias of the blood, erythroblastosis and anemia of the newborn, leukemia, etc. Data on prematurely born infants likewise are excluded as far as possible, but in some instances the records of weight at birth and term of gestation of infants born at home are not absolutely reliable. Many of the lowest values in the charts represent samples of blood taken from frankly anemic infants who subsequently were treated with iron and were observed over a long period, during their recovery from the anemia; the data obtained on those infants after the administration of iron will be dealt with in later communications.

As a considerable proportion of the samples of blood listed here were drawn from infants who were in hospital wards and outpatient departments because of various ailments, it may be said that the statistics so assembled do not fairly describe a representative cross section of the total child population of Cincinnati. The observations taken as a whole are in fact probably somewhat overloaded with data on infants who were predisposed to or were having varying degrees of nutritional anemia. Better data for the establishment of desirable hematologic standards for normal children probably could be obtained from the study of rigorously selected groups of infants fortunate enough to have received the best prenatal and postnatal care, breast feeding and well balanced diets and to have escaped the hazards of intercurrent infections. For example, the group of infants studied from this point of view by Faxén [5] in Göteborg, Sweden, was probably the most carefully selected of all reported. It is significant that the values for hemoglobin in the whole blood in that group were uniformly higher than values which have been reported by various investigators in other countries. Investigations limited strictly to seemingly normal children, however, fail to furnish additional information that is needed in general

5. Faxén, N.: Red Blood Picture in Healthy Infants, Acta pædiat. (supp. 1) **19**:142, 1937.

pediatric practice: namely, that which concerns the abnormal divergences from arbitrarily selected standards which can occur in children living under unfavorable conditions. The need for full recognition of those divergences is responsible for our assembling observations from a wide range of experience with divers types of subject.

METHODS

The samples of blood were all obtained by venipuncture, the external jugular vein and veins of the scalp, arm and ankle being used most often and the longitudinal sinus rarely. The blood was transferred from the syringe to a small vial containing a suitable amount of dried heparin, and determinations of the volume of packed cells, number of cells and hemoglobin content of the heparinized whole blood were carried out as described in the previous paper.[4] The amount of heparin depended on the anticoagulant potency of various preparations used in the course of several years but was usually in the proportion of 1 or 2 mg. to 5 cc. of blood.[6] The method of derivation of the respective values for the cells is displayed

Data on Blood of a Normal Four Year Old Child, Illustrating the Terminology and Method of Derivation of the Values Calculated for the Cells

		Symbols*
Values determined for whole blood:		
A. Red cell count, millions per cubic millimeter	4.69	$\overline{M}$
B. Volume of packed red cells, percentage	39.3	%
C. Hemoglobin, grams per hundred cubic centimeters	13.5	Gm. %
Values calculated for red cells:		
Mean red cell size (B × 10 ÷ A), cubic microns	84.0	μ^3
Hemoglobin concentration (C ÷ B × 100), grams per hundred cubic centimeters packed cells	34.4	Gm. %
Mean hemoglobin content per cell (C × 10 ÷ A), micromicrograms	28.8	$\gamma\gamma$

* Used in the figures.

in the table. The term "mean cell volume," used in the previous paper, has been changed to "mean red cell size," a designation which has the advantage of being less easily confused with reference to the volume of cells in whole blood. Simplicity of expression has been sought in the final adoption of these terms, which have caused the least confusion in our discussions with persons unfamiliar with the technic.

Data on the volume of cells in whole blood are not presented here because they would add little to the information on cell counts and mean red cell size.

When the histograms were prepared, the frequency distributions of the several sets of values were first arranged and examined in 22 groups, which represented shorter age periods than those shown here. To simplify the charts, those groups which showed closely similar patterns of mode and span were then combined to form larger groups of data, which represented the 9 age periods indicated in charts 2, 4, 6, 8 and 10. The combining of the groups seemed to emphasize rather than to change in any way the conclusions concerning the frequency distributions of the values observed in the different age periods and concerning the direction and magnitude of the shifts in distribution which occurred with changing age.

6. Until late in 1936, the heparin used in these studies was that prepared by Hynson, Westcott and Dunning, Baltimore. Since that time a more potent product, prepared according to the methods of E. Jorpes, has been obtained from Apoteksvarucentralen, Vitrum, Stockholm, Sweden.

OBSERVATIONS

Red Blood Cell Counts (charts 1 and 2).—In 34 samples of blood from the umbilical cord the mean red cell count was 4,800,000 per cubic millimeter, with individual counts distributed between 3,800,000 and 6,000,000. During the first few days of life the cell counts tended to increase, and in 89 samples of blood taken during the age period of from 1 to 10 days the mean cell count was 5,200,000, with individual counts varying from 3,800,000 to 7,000,000. Increases in cell count

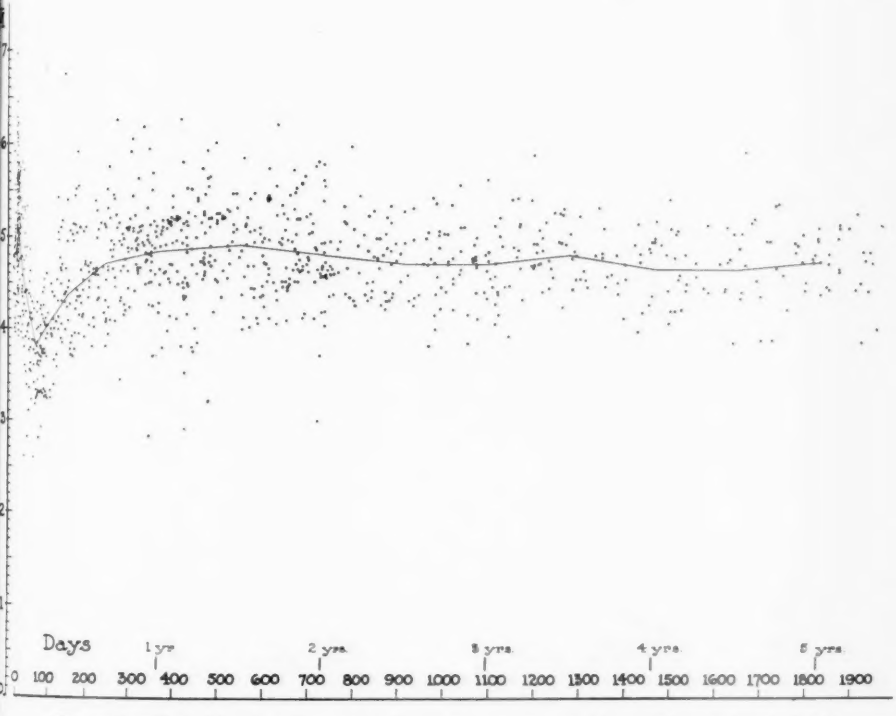

Chart 1.—Red blood cell count (in millions per cubic millimeter) of 1,070 samples from infants at ages ranging from birth to 5¼ years. In this and the following scatter charts, the solid line represents the averages of values found in the different age periods. These averages are represented also in chart 13.

might have been due partly to dehydration in some of the infants, who received too little fluid during this period (the increase of hemoglobin in the whole blood shown in charts 5 and 6 is in keeping with this conclusion), but charts 3, 4, 7 and 8 give evidence that new cells were entering the circulation at this time, that is, smaller cells, in which the concentration of hemoglobin was higher. After the first ten days of life the number of cells in the blood diminished rapidly, and in 88

samples from infants aged from 30 to 90 days the mean red cell count was 3,800,000, with individual counts distributed between 2,400,000 and 5,400,000. After the age of about 2 months the cell counts increased, attaining a mean value of 4,800,000 at the end of the first year; they remained approximately at this average value during the remainder of

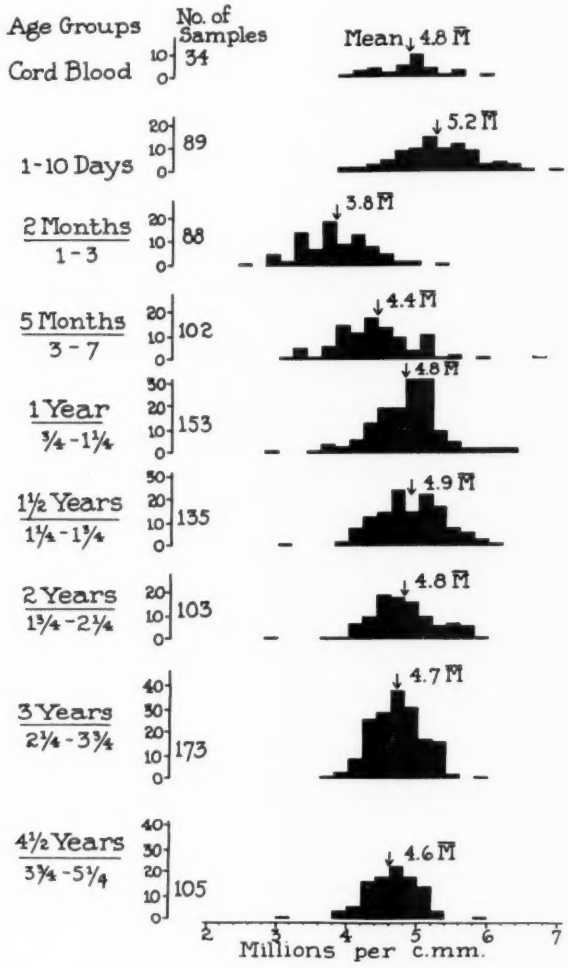

Chart 2.—Red blood cell counts; frequency distribution of values for infants in different age periods.

the five year period. The greatest variability in the cell counts (widest scatter in chart 1) was found at ages ranging from 6 to 18 months; this variability was less marked after the end of the second year and decreased further in the fourth and fifth years.

Mean Red Blood Cell Size (charts 3 and 4).—In the 34 samples of blood from the umbilical cord the average of the values for mean red cell size was 113 cubic microns, with the values for individual samples distributed between 90 and 124 cubic microns. Immediately after birth the erythrocytes diminished in size, to reach an average value of 73 cubic microns at the age of 8 months and about 72 cubic microns in the first half of the second year. At about the age of 8 months, values below 70 cubic microns began to appear with increasing

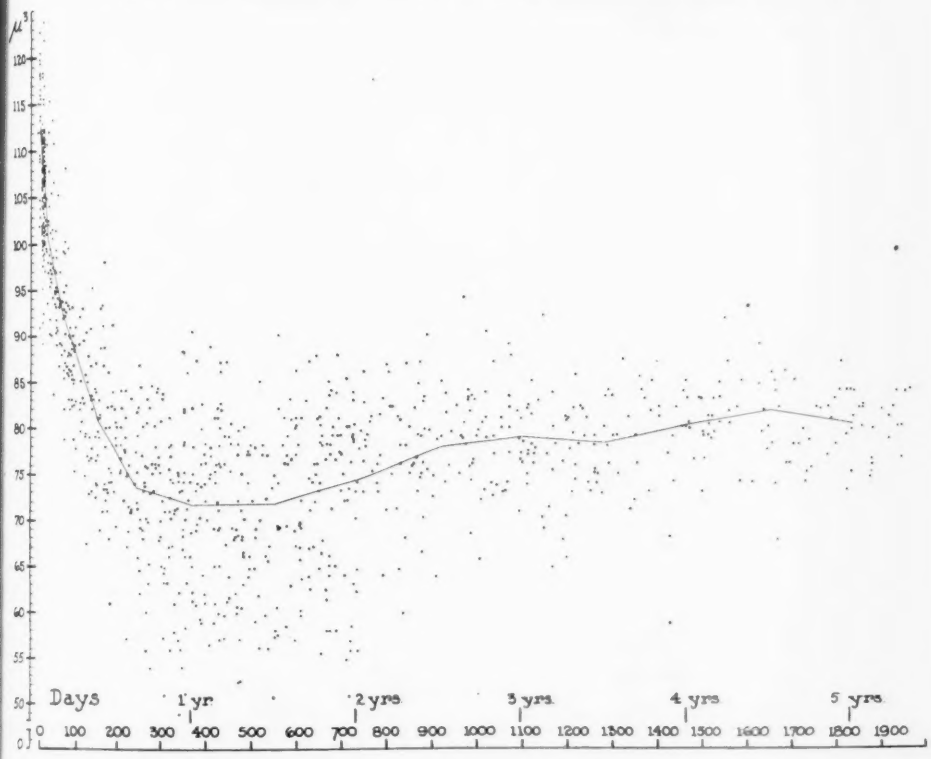

Chart 3.—Mean red blood cell size (in cubic microns) of 1,070 samples from infants at ages ranging from birth to 5¼ years.

frequently; at 9 months the tendency toward lower values was more pronounced, and the frequent occurrence of marked microcytosis continued through the second year. The infants with values below 60 cubic microns often had clinically recognizable anemia, but it is important to note that anemia had not been suspected in a great many of the infants whose red blood cells were found to be of this size or smaller. Since the development of such a degree of microcytosis was limited for the most part to the age period between 8 and 27 months, this period may be properly described as the most critical for the development of micro-

cytic anemia. After the end of the second year of life the scatter, or variability, in the values for cell size rapidly diminished. Symmetric distribution of these values within a narrower range may be seen in chart 4 which represent the values found at 3 and at 4½ years, respectively.

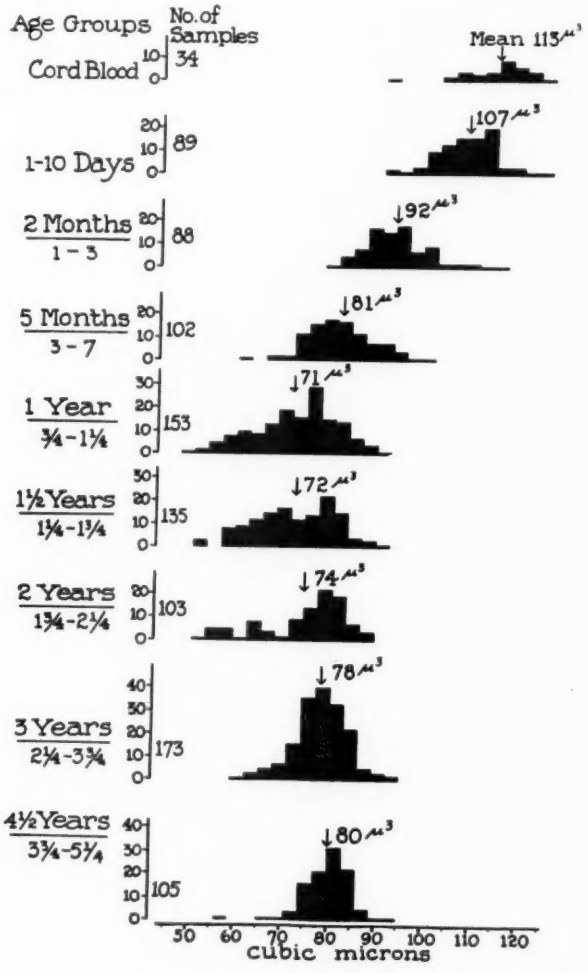

Chart 4.—Mean red blood cell size: frequency distribution of values in different age periods.

Hemoglobin in Whole Blood (charts 5 and 6).—The mean of the values for the hemoglobin content of 34 samples of blood taken from the umbilical cord was 17.9 Gm. per hundred cubic centimeters, the individual values being distributed between 13 and 22 Gm. During the first few days of life these values increased. In 89 samples obtained

during the first ten days, the mean hemoglobin content was 19 Gm. per hundred cubic centimeters, with individual values distributed between 14.5 and 25 Gm. Again it should be noted that, as observed in the description of the increased cell counts found during this period, such increases might have been due partly to increased concentration of the blood in cases in which mild dehydration occurred. That these changes were not due to concentration of the blood alone, however, is indicated by the data in charts 3, 4, 7 and 8, which give evidence that the increase in cell counts was due at least in part to the fact that new types of cells were appearing in the blood at this

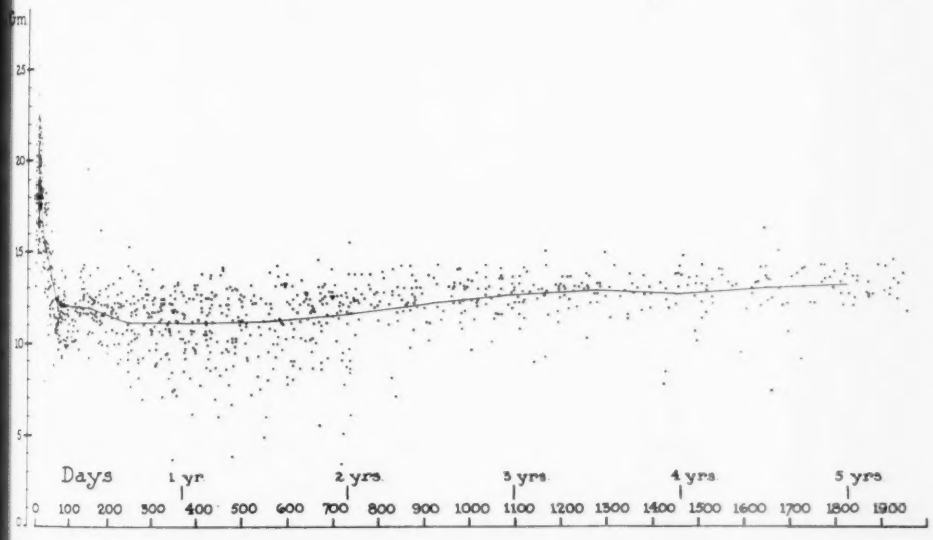

Chart 5.—Hemoglobin (in grams per hundred cubic centimeters) in 1,070 samples of whole blood from infants of ages ranging from birth to 5¼ years.

time, cells which were smaller and tended to have higher concentration of hemoglobin. After the first few days of life the average values for hemoglobin in the whole blood decreased rapidly for about two months, then more slowly through the rest of the first year and the first half of the second year. In 135 specimens obtained from infants at ages around 1½ years (16 to 21 months, inclusive) the mean hemoglobin content of the whole blood was 11.1 Gm. per hundred cubic centimeters, with values distributed between 3.5 and 14.5 Gm. After the infants reached ages around 20 months, the low values were found less frequently, and the average values increased slowly, to reach 12.8 Gm. in the infants around 4½ years of age.

At any age, values below 10 Gm. of hemoglobin per hundred cubic centimeters of whole blood can be assumed to indicate a degree of

anemia ranging from moderate to severe. The significance of values around 11 Gm., the average of the group at the age of 18 months, is more difficult to gage; but even this certainly does not represent a level that can be accepted as normal. It is probable that an average value around 12.5 Gm., such as was found in the optimum group of infants in their second year (chart 13), may be considered desirable at

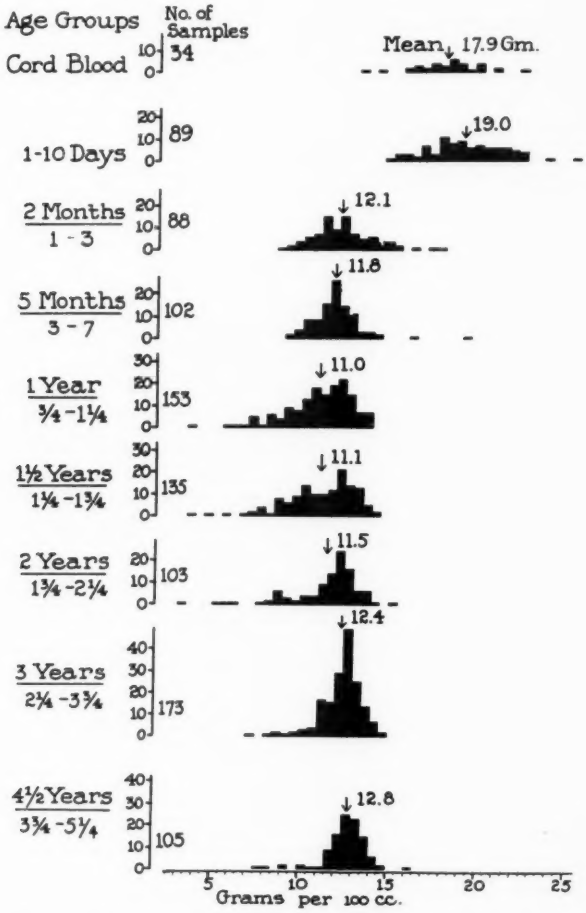

Chart 6.—Hemoglobin in whole blood: frequency distribution of values in different age periods.

this age. In any case, the values below such average, or desirable, levels, as found at different ages, can be cited to demonstrate the relative tendencies shown by these infants to have varying degrees of anemia at those ages. Since changes in number, size and hemoglobin concentration of the red cells complement each other in affecting the amounts of hemoglobin contained in whole blood, these separate factors should

be borne in mind while one is examining the distribution patterns of the values illustrated in charts 5 and 6. Values below 10 Gm. of hemoglobin per hundred cubic centimeters of whole blood were found most frequently first at ages ranging from 1 to 3 months, when the cell counts tended to fall to lowest levels, and again at ages ranging from about 8 months to 2½ years, when the cells decreased most in size and hemoglobin content. The values below 8 Gm. per hundred cubic centimeters, indicating severe anemia, were practically all found in children of the latter age period.

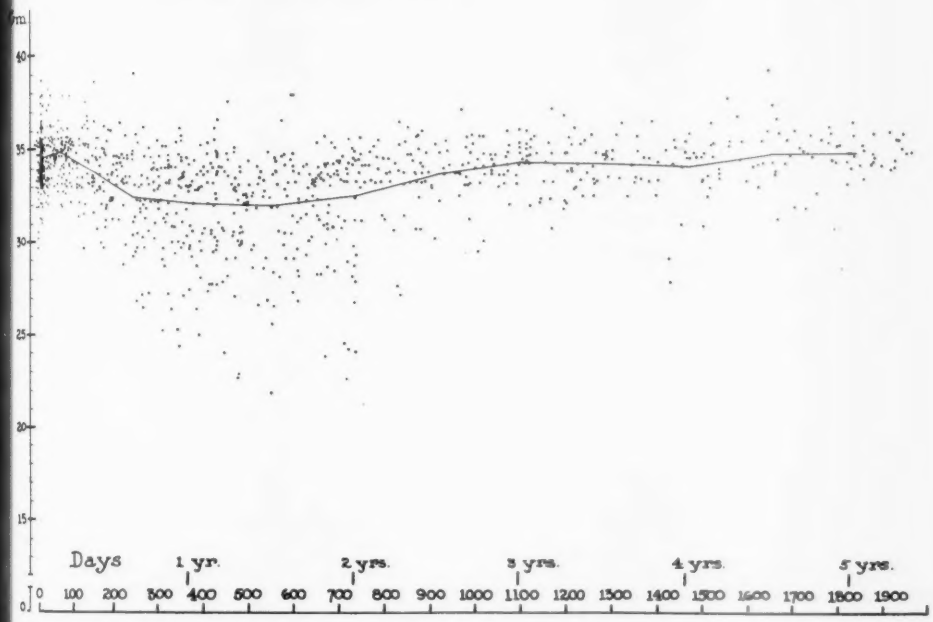

Chart 7.—Hemoglobin concentration (in grams per hundred cubic centimeters) in red blood cells of 1,070 samples from infants of ages ranging from birth to 5¼ years.

The narrowest range of variability from the mean in these data may be seen at about the age of 5 months and after the third year. The distribution pattern of the data at about the age of 5 months (4 to 6 months inclusive) is especially interesting because of the different factors which influenced these findings. In the blood of most of the infants examined during this age period, the cell counts were found to be increasing, after having fallen to low levels in the second month. The mean size of the red cells was decreasing, and as a rule it decreased more in the succeeding months. The concentration of hemoglobin in the cells (charts 7 and 8) in the second month had increased considerably above the concentration found at birth; but at

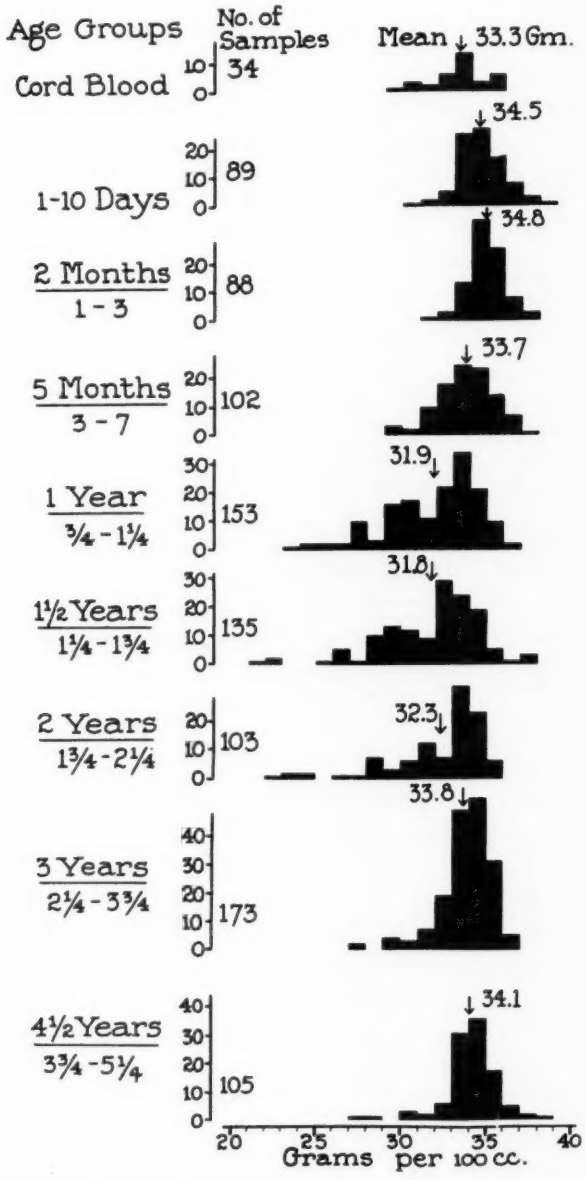

Chart 8.—Hemoglobin concentration in red blood cells: frequency distribution of values in different age periods.

about the fifth month these values were decreasing, and they decreased still further in the succeeding months. Thus the fifth month of life in this group of infants appeared to be a turning point, at which the values for hemoglobin in whole blood became constant within fairly narrow limits but beyond which the hemoglobin values showed a high degree of variability until the end of the third year.

Hemoglobin Concentration in the Red Blood Cells (charts 7 and 8).—The mean of the hemoglobin concentration in the red blood cells

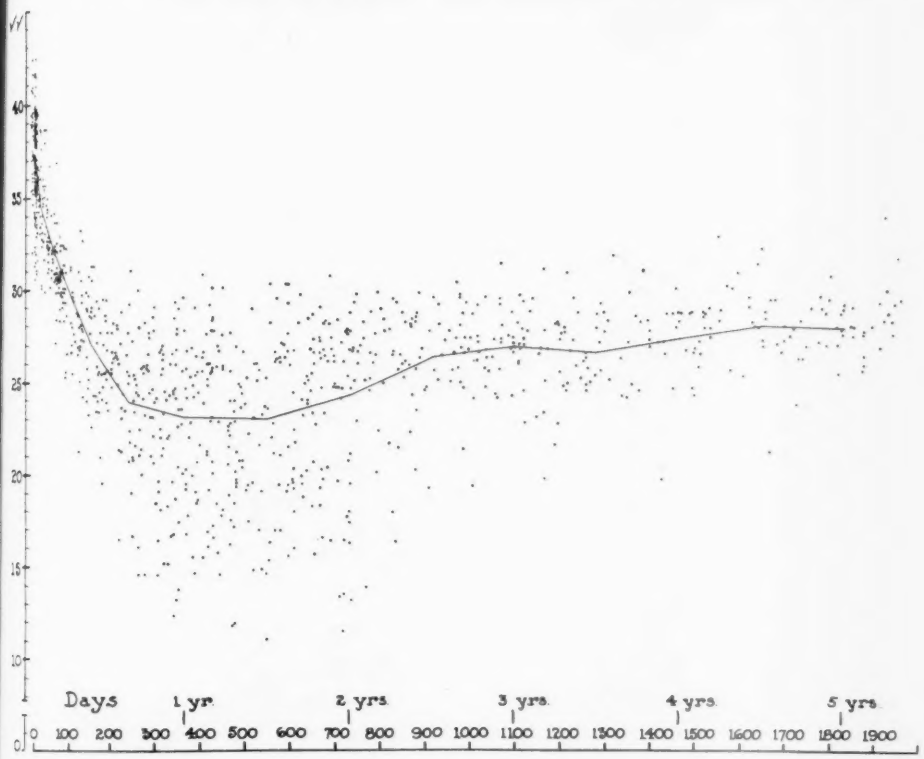

Chart 9.—Mean hemoglobin content (in micromicrograms) per red blood cell of 1,070 samples from infants of ages ranging from birth to 5¼ years.

of 34 samples of blood from the umbilical cord was 33.3 Gm. per hundred cubic centimeters of packed cells, the individual values being distributed between 29 and 35.9 Gm. These values tended to increase during the first and second and often through the third month of life; thus in the red cells of 88 specimens from infants at ages ranging from 30 to 90 days, the mean of the hemoglobin concentration was 34.8 Gm., with individual values varying from 31 to 37.9 Gm. The values thereafter tended to diminish, the lowest average being found during the second year. In 135 samples from infants about 1½ years of age,

the mean hemoglobin concentration of the cells was 31.8 Gm., with individual values varying from 21 to 37.9 Gm. The values below 28 Gm. were practically limited to the age period from 8 months to 2½ years, which may therefore be described as the most critical for the development of hypochromic anemia.

Mean Hemoglobin Content per Red Blood Cell (charts 9 and 10).—The values for the mean hemoglobin content per cell are, of course,

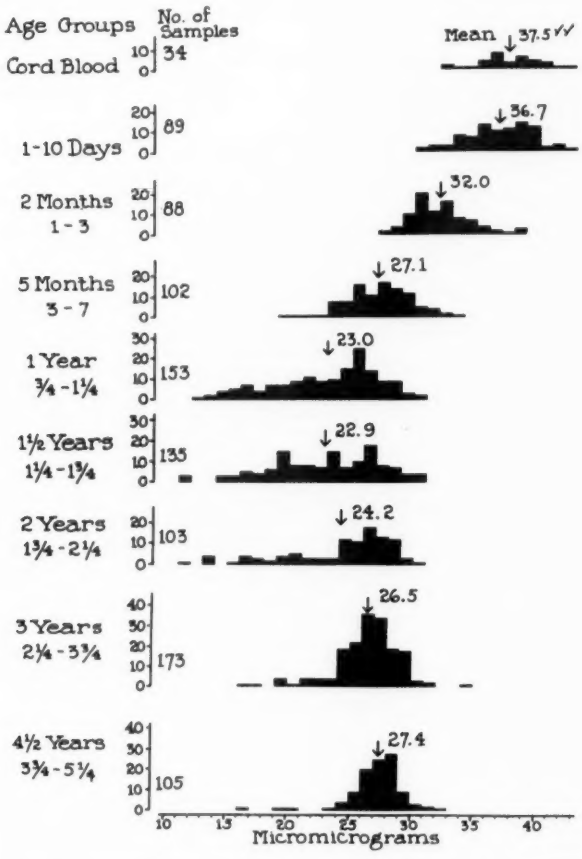

Chart 10.—Mean hemoglobin content per red blood cell: frequency distribution of values in different age periods.

dependent on both the size and the hemoglobin concentration of the cells. Thus the distribution patterns of the values shown in charts 9 and 10 constitute a summation of the cellular changes demonstrated in charts 3, 4, 7 and 8. The distribution of values at ages ranging from about 8 months to 2½ years (chart 9) again delineates this period as the most critical for the development of microcytosis and hypochromia

of the erythrocytes in the majority of these infants. During the first six months of life the mean size of the cells in most cases diminished, without a significant decrease in the hemoglobin concentration of the cells; but after six months the tendencies to microcytosis and hypochromia both contributed to the increasingly frequent occurrence of

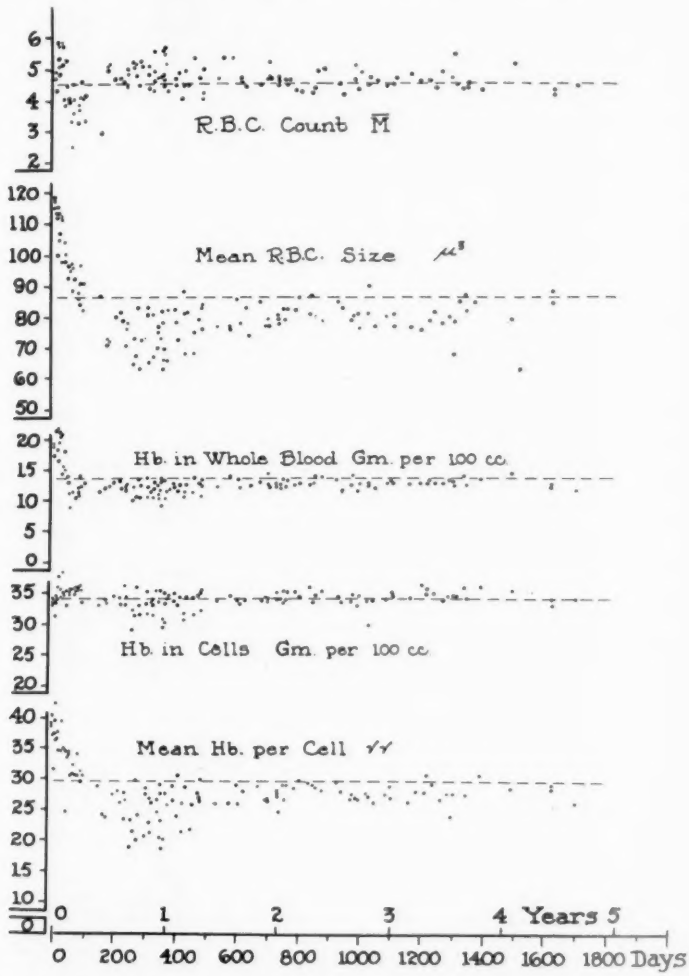
R.B.C. Count M
Mean RBC. Size μ³
Hb. in Whole Blood Gm. per 100 cc.
Hb. in Cells Gm. per 100 cc.
Mean Hb. per Cell γγ
0 1 2 3 4 Years 5
0 200 400 600 800 1000 1200 1400 1600 1800 Days

Chart 11.—Data on 144 samples of blood from infants in the optimum group, selected from families of upper economic levels. In charts 11 and 12 the broken lines represent average values for well children at ages around 4 and 5 years.

low values for the mean hemoglobin content per cell, which was most pronounced in the middle of the second year.

Optimum and Institutional Groups (charts 11 and 12).—Data on 144 samples of blood obtained from the favored, healthy infants who

were described in the introductory paragraphs as a selected optimum group are represented in chart 11, while data on 67 samples from a group of infants living in an orphanage are represented in chart 12. Closely similar data on infants in another such institution have been assembled, but for the present purposes it seems sufficient to present

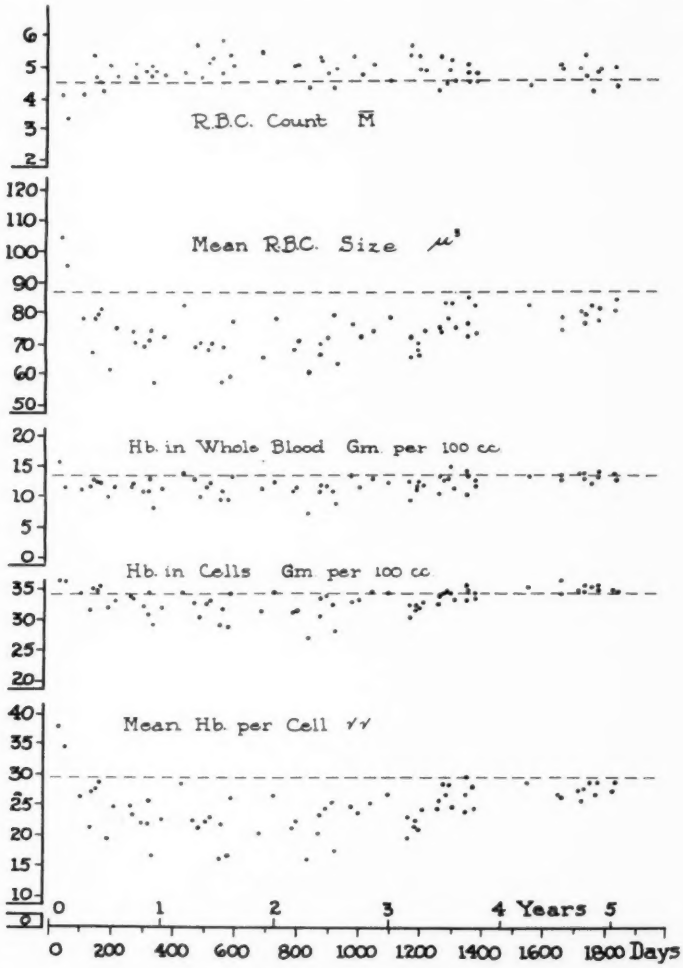
R.B.C. Count M
Mean R.B.C. Size μ³
Hb. in Whole Blood Gm. per 100 cc.
Hb. in Cells Gm. per 100 cc.
Mean Hb. per Cell γγ
0 1 2 3 4 Years 5
0 200 400 600 800 1000 1200 1400 1600 1800 Days

Chart 12.—Data on 67 samples of blood from a group of seemingly well infants living in an orphanage.

here only one of these charts. The distribution patterns of the data on the optimum and the institutional group, respectively, showed little discernible difference in the first eight or ten months of life; but after the first year the values for size and hemoglobin content of the cells, as well as those for the hemoglobin content of the whole blood, were

consistently higher in the optimum group. There was little difference between the average cell counts in the two groups at any age.

For several of the infants represented in the optimum group iron therapy was started at about the age of 9 months, when moderately low values for size and hemoglobin content of their red blood cells were found (chart 11). These infants, although exhibiting no recognizable physical signs of anemia, showed prompt improvement in blood values, comparable to that obtained in the cases of borderline anemia which were cited in the previous paper.[4] The infants in the institutional group who at various ages had significantly low values for hemoglobin and size of red cells likewise were given iron, with excellent results. The improved values obtained after the administration of iron in these cases will be reported later.

The reasons for the differences in these two groups are obscure, but it is hoped that they can be traced in later analyses of various influences affecting these infants. The institutional children were well cared for and apparently were offered a varied diet about as early as most of the infants in the optimum group. It seems doubtful, therefore, that differences in the diets offered the two groups of infants can alone explain the higher incidence of anemia in the institutional group. The greater exposure to and incidence of intercurrent infections in the institution, where many children live in close contact with one another, may be suggested as a possible factor leading to anemia. Another predisposing factor in this group may be the health of the mothers during the prenatal period. These mothers were from poorer families, and most of them were young unmarried girls, having probably a greater tendency to anemia (or at least lower reserves of iron) than the mothers of the optimum group of infants.

Averages (chart 13).—The averages of data on the 1,070 samples of blood from which the scatter charts were prepared are represented in chart 13. For comparison, averages of the data on 144 samples from the optimum group of infants (chart 11) are indicated by dotted lines. The curve representing the average red cell count in the optimum group is not significantly different from that of the entire series. The curves indicating changes of the mean red cell size in the two groups are practically identical up to the age of 8 months, after which the values in the optimum group increase, being considerably higher in the second year. The curves show less divergence in the third and fourth years, when the average values for the entire series increase. The values for the hemoglobin in whole blood in the two groups are practically identical during the first two months of life, but at 18 months the average for the whole group is 11.1 Gm. per 100 cc., while that of the optimum group is 12.7 Gm. At 4½ years the curves representing the

averages of these values in the two groups again meet, at the higher level. The average values for hemoglobin concentration in the cells in the two groups are identical during the first few days of life and nearly so during the first eight months; but after that the average values in the optimum group are 1 to 2 Gm. higher than those of the entire series. The differences between the averages of the mean hemoglobin content per cell in the two groups represent a summation of the differences observable in the curves which represent changes in cellular size and hemoglobin concentration.

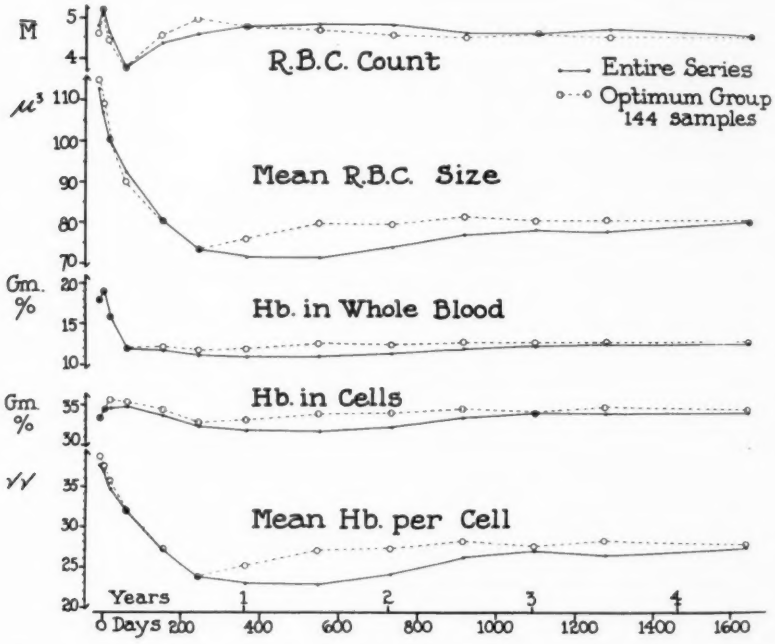

Chart 13.—Averages of data on the 1,070 samples of blood represented in the scatter charts (charts 1, 3, 5, 7 and 9). The broken lines represent averages of data on 144 samples from the optimum group (chart 11) of infants, who were reared under favorable circumstances in families of upper economic levels.

COMMENT

The most important information conveyed by these charts is probably that which defines the critical age periods in which notable changes in character of the red blood cells are likely to occur. Under any circumstances the average life of erythrocytes is fairly short,[7] and the maintenance of the red cell count and hemoglobin levels within their usual narrow limits of variation in the blood depends on delicate adjust-

7. Isaacs, R.: Formation and Destruction of Red Blood Cells, Physiol. Rev. **17**:291 (April) 1937.

ments between the extremely active processes of cellular generation and degeneration. The tendencies for the circulating cells to be replaced by new cells which are similar or dissimilar in type—(larger or smaller, and with greater or lesser concentrations of hemoglobin)—must be interpreted with due regard for many different conditions of nutrition and growth which may affect the development of the erythrocytes in individual infants at different ages. The association of microcytosis and hypochromia of the erythrocytes with nutritional anemia is easily demonstrated, but further experience is needed to determine just how closely the intermediate types of cells are associated with various phases of infantile development, healthy and otherwise.

In the group of infants here described, the finding of microcytosis and hypochromia of red blood cells became increasingly frequent among infants as their ages increased from 8 to 18 months. The values for these characteristics of the erythrocytes during the second year, however, were not evenly distributed between the upper and lower limits of the several groups of observations. In charts 4, 8 and 10, the histograms representing 135 samples obtained from infants at ages around 1½ years (16 to 21 months, inclusive) show a distinct bimodality, indicating that a considerable proportion of this group of infants tended to have either relatively high or relatively low values for size and hemoglobin content of the erythrocytes, compared with the average of the group at this age. The factors which determine the bimodal tendencies in these data will receive further study, but it should be noted in passing that the clinical courses of the infants in these groups with high and low values may follow distinctly different paths.

The suddenness of disappearance of marked microcytosis and hypochromia of the red blood cells after the second year of life deserves as careful consideration as does their increasing frequency in the earlier age periods, when so many cases of nutritional anemia are developing. The changed pattern of the findings after the second year might be due simply to the increased ingestion of varied diets, which naturally furnish more iron and other substances needed in formation of cells and hemoglobin. On the other hand, in some of the infants of this group, who have been followed closely from birth, the varied diets that were offered early (and apparently taken well) did not prevent the development of anemia; in anemic infants, moreover, changes in diet alone usually fail to bring about rapid improvement. In addition to dietary factors which could lead to improved erythrogenesis, certain physiologic adjustments concomitant with growth in the third year can be postulated: stabilization of gastric, intestinal and hepatic functions, through which hemopoietic factors may be derived; the slowing up in rate of body growth, and the increase of bone marrow.

Other factors possibly concerned in the disappearance of the low values after the second year may be described as artificial rather than natural circumstances. Mild signs of anemia often fail to be recognized in infants in whom this condition is slowly developing at the end of the first year of life; but later on, at ages ranging from 18 to 20 months, the anemia in these infants reaches a stage at which the clinical diagnosis becomes increasingly easy, even without the aid of laboratory tests. Many such infants who came under our observation for the first time at ages over 2 years already had received appropriate iron medication, but since those treated with iron are excluded from this report, the rising values found for them do not appear in the charts. Another artificial factor, difficult to evaluate, which may significantly contribute to this abrupt disappearance of low values, is that a number of the anemic infants die of various infections at this age and hence no longer carry their low values into the older age periods. Hospital records disclose many such cases, and it is possible that more could be found among infants who die at home of various diseases under conditions in which diagnosis of the anemic condition is not made.

In routine clinical practice, the hemoglobin content of whole blood is commonly deemed a satisfactory criterion of the presence or absence of anemia; this has been true also in many extensive investigative studies of nutritional anemia reported during recent years. In many instances, however, the determination of hemoglobin in whole blood alone is inadequate to demonstrate the development of the anemic condition, especially in its early stages. In the series of observations here reported, the general average of the values for hemoglobin in whole blood reached its lowest level, 11.0 Gm. per hundred cubic centimeters, at the end of the first year and remained practically at that level during most of the second year (charts 5 and 13). This average level was sustained by virtue of the fact that the red blood cell count was high in most of the infants in whom anemia developed at this age, the increased number of cells compensating for the decreasing amount of hemoglobin contained in those cells. An example of such findings in a typical case of mild anemia at this age was cited in table 3, example 5, of the previous paper,[4] the red cell count being 6,230,000, the mean red cell size 59 cubic microns, the hemoglobin in whole blood 10 Gm. per hundred cubic centimeters, the hemoglobin concentration in packed red cells 27.6 Gm. per hundred cubic centimeters and the mean hemoglobin content per cell 16.2 micromicrograms. Most of the infants at ages ranging from about 9 months to 2 years represented in chart 1 of the present paper as having cell counts above 5,500,000 were of this type, their red blood cells showing marked microcytosis and hypochromia while the hemoglobin in the whole blood was only moderately low. In

such cases the values for hemoglobin in whole blood, which are within supposedly normal limits or are only moderately low, do not aid the early diagnosis of nutritional anemia when considered alone as much as do the values for mean size and hemoglobin content of the cells.

SUMMARY

In this paper data are presented on 1,070 samples of blood from 615 white infants and children, at ages ranging from birth to 5¼ years, who had never received iron other than that in their diets. The observations are assembled from a wide range of groups and types of subjects, healthy and otherwise, anemic and nonanemic, but excluding prematurely born infants and those with primary blood dyscrasias. Values for the red cell counts, mean red cell size (in cubic microns), hemoglobin content of whole blood, hemoglobin concentration in packed red cells and mean hemoglobin content per cell are presented in scatter charts and histograms. The distribution patterns of the data show the age periods in which notable changes in character of the erythrocytes were found and the relative frequency with which varying degrees of anemia occurred in these infants at different ages. Values below 10 Gm. of hemoglobin per hundred cubic centimeters of whole blood were found most frequently, first, at ages ranging from 1 to 3 months, when the red cell counts tended to fall to lowest levels, and again at ages ranging from 8 months to 2½ years, when the size and hemoglobin content of the red cells decreased most. The most critical age for the maximum development of microcytosis and hypochromia of the erythrocytes (characteristic of nutritional anemia) was about 18 months.

HUMAN PASSIVE TRANSFER ANTIBODY

III. SERIAL TITRATIONS ON TREATED AND UNTREATED PATIENTS WITH HAY FEVER

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Because of its relative frequency and clearly defined seasonal incidence, hay fever has been studied by immunologic methods more often than other allergic disorders which manifest sporadic symptoms. Nevertheless, there are available only limited and contradictory data concerning normal fluctuations and the effect of treatment on the passive transfer antibody titer.

A technic for titration of passive transfer antibody by neutralization, which we previously reported,[1] appeared to offer another and perhaps more exact method of approach.

The purpose of this investigation was to determine by serial titrations the fluctuations of passive transfer antibody titer in treated and untreated patients with hay fever. The relation of the titer to the amount of previous treatment and the intensity of clinical symptoms was also recorded.

METHOD AND SUBJECTS

Titration.—The method of titration was described in detail in a previous report.[1] It is briefly as follows: 1. A series of mixtures of constant amounts of the patient's serum with decreasing amounts of antigen is prepared. 2. After storage overnight in the refrigerator, the mixtures are injected intracutaneously into 3 normal recipients. 3. After the lapse of twenty-four to forty-eight hours, the test is performed by means of a single intramuscular injection of a strong concentration of antigen. 4. Within a period of twenty minutes to two hours, wheal and erythema reactions occur only at the sites prepared with underneutralized mixtures. The titer of passive transfer antibody is read as the first nonreacting site and is recorded in terms of the antigen concentration required for neutralization.

A system of recording titer in units has been employed according to which 1 unit of passive transfer antibody is that amount which is neutralized by

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Read in part at meetings of the Pediatric Section of the New York Academy of Medicine, Dec. 10, 1936, and the Society of Pediatric Research, May 3, 1937.

1. Lippard, V. W., and Schmidt, W. M.: Human Passive Transfer Antibody: I. Titration by Neutralization, Am. J. Dis. Child. **54**:288 (Aug.) 1937.

0.00001 mg. of antigen nitrogen per cubic centimeter of mixture. The potency of antigen in terms of nitrogen content may depend on the method of preparation, and the results cannot be compared with those obtained with a different preparation. One set of pollen extracts was used for consecutive tests throughout this study.[2]

Subjects.—Subjects were patients in the outpatient department; with the exception of 2 adults, they ranged in age from 2½ to 12 years. Eighteen patients who received preseasonal pollen injections comprised the treated group. Of these, 15 had previously been untreated, 1 had had a few injections and 2 had had full courses of treatment during the preceding season.

Ten patients who received no treatment formed the control group. Of these, 7 gave a history of definite hay fever; 3 hypersensitive persons gave no history of hay fever but showed passive transfer antibody for ragweed or timothy on routine testing.

PLAN OF STUDY

Titrations were performed during four periods: (1) on admission to the clinic, from November 1935 to June 1936; (2) at the beginning of the season of pollination (in the case of the ragweed-sensitive patients, from July 1 to August 15; in the case of the grass-sensitive patients, from May 12 to June 6); (3) at the termination of the season of pollination, from September to December; (4) from five to six months after the termination of the season of pollination and cessation of treatment, in March and April 1937.

Clinical symptoms were noted at each visit to the clinic, data being obtained both from examination and from statements of the patient and the parents. In addition each patient kept a daily record of symptoms on a standard form. The severity of symptoms during the current season was compared with that of previous seasons, as estimated on the same basis from information contained in the history and in statements of the patient and the parents.

RESULTS

Effect of Treatment and of Exposure to Atmospheric Pollen on Antibody Titer.—The results of all titrations are summarized in table 1. With the exception of 2 patients who received a full course of treatment before the previous season, the initial titers of the treated group ranged from 3 to 300 units. The titers of patients selected for the control group fell within the same range.

Preseasonal titrations were done on the untreated control patients after a lapse of one and one-half to five months. No significant or consistent change in titer was noted. In 6 patients the titer remained constant; in 3 it showed a slight increase and in 1 a slight decrease.

On the other hand, 16 of 18 treated patients showed a distinct rise in titer after treatment for two to ten months. In this group, those who responded to the injections of pollen extract with some rise in titer showed a range of 150 to 6,000 units.

2. The pollen extracts used in this investigation were obtained from the Arlington Chemical Company, Yonkers, N. Y.

It seems apparent from these data that injection of pollen extracts is followed by a significant increase in the antibody titer with considerable regularity and that in the absence of injection or other contact with pollen the titer tends to remain fairly constant for months. The results of the initial and preseasonal titrations are presented graphically in chart 1.

The third titration, performed at the termination of the season of pollination, revealed a rise in titer in every control patient. The increase was moderate, the titers ranging from 60 to 600 units.

TABLE 1.—*Passive Transfer Titers on Patients with Hay Fever*

Treated Patients					Untreated Controls				
	Titers					Titers			
Case No.	Initial	Pre-seasonal	Post-seasonal	5-6 Mo. After Treatment and Exposure	Case No.	Initial	Pre-seasonal	Post-seasonal	5-6 Mo. After Exposure
1	3	3	3	3	1	3	3	60	3
2	3	3	3	3	2	3	3	60	30
3	3	150	...	30	3	30	30	150	60
4 (O)	3	150	...	...	4	30	30	60	30
5 (T)	3	300	600	...	5	30	30	60	60
6	3	300	300	150	6	30	60	600	600
7	30	300	300	60	7	150	150	300	150
8	60	150	1,500	600	8	150	60	150	30
9	60	300	600	300	9 (T)	150	300	600	...
10	60	600	1,500	600	10	150	300	600	600
11	150	600	1,500	...					
12	150	600	.....	...					
13	150	1,500	1,500	600					
14*	150	1,500	1,500	1,500					
15	150	1,500	.....	300					
16	300	6,000	1,500	3,000					
17†	600	3,000	3,000	1,500					
18†	600	4,500	6,000	.....					

* A small amount of treatment was given the previous season.
† A full course of treatment was given the previous season. All other patients were previously untreated.
T indicates that the patient was hypersensitive to timothy, and O, to orchard grass. All other patients were sensitive to ragweed.

Fourteen treated patients were obtained for titration at this time; 1 failed to reappear and 3 did not return until from one to two months after the cessation of treatment. In 6 of these patients the titer showed some further increase, in 7 it remained at the same level and in 1 it decreased.

The postseasonal titrations, therefore, afforded evidence that during a period of exposure to atmospheric pollen the titers of control patients increased moderately. Little further increase over the relatively high levels attained at the time of the preseasonal titrations was noted in the treated group.

Samples were again taken for titration from five to six months after termination of the season and cessation of treatment. In 6 of the 9 control patients the titer decreased, and in 3 it remained constant. Of

the 13 treated patients on whom titrations were done at this time, 9 showed a decrease in titer and 3 showed no change.

Although both the treated and the control series showed a decrease in antibody titer after cessation of contact with pollen, in neither group did the mean fall to its original level. It would have been desirable to obtain a fifth titration just before the onset of the next season of pollination, from eight to nine months after the cessation of contact with pollen. This was impossible, in view of the necessity of beginning preseasonal therapy for the season of 1937.

The variations of mean titer in the two groups, with relation to the season, are shown in chart 2.

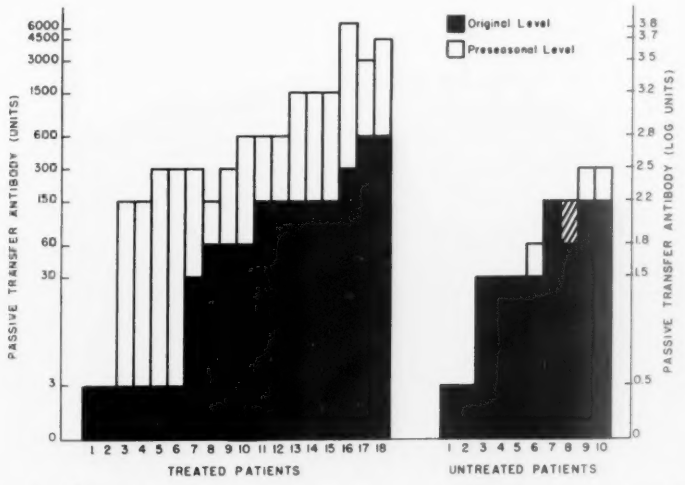

Chart 1.—Original and preseasonal titers of passive transfer antibody in treated and untreated patients with hay fever.

Relation of the Amount of Treatment to Titer and to Clinical Results.—The relation of the amount of treatment to the titer was studied in 16 of 18 treated patients. Two patients were not available because they were treated by outside physicians and the amount of treatment could not be ascertained with certainty. All other patients were treated by subcutaneous injections of increasing doses of pollen extracts at one to three week intervals, depending on the date of admission to the clinic. The initial dose in most cases contained 0.0002 mg. of nitrogen.

In table 2 are recorded the total amount of treatment (expressed in milligrams of antigen nitrogen administered during the preseasonal course of treatment), the initial and preseasonal titers and the severity of clinical symptoms during the previous and the current season.

It is apparent that high and low preseasonal titers were evenly distributed with both the high and the low range of total antigen administered. Furthermore, both good and poor results occurred with the high and with the low range.

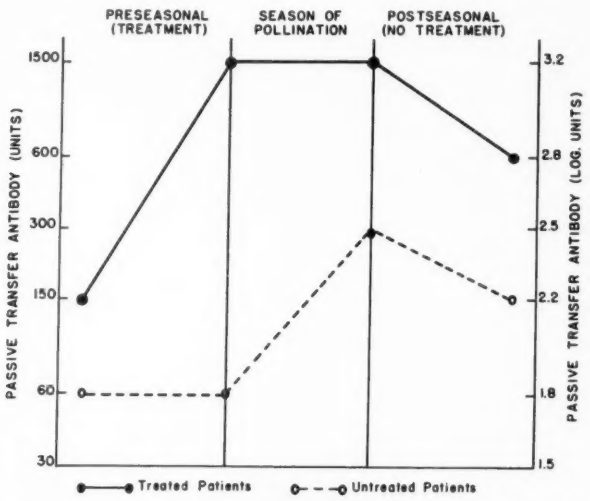

Chart 2.—Variations in the mean titer of passive transfer antibody in treated and untreated patients with relation to treatment and season of pollination.

TABLE 2.—*Amount of Treatment in Relation to Titer and Clinical Symptoms**

Case No.	Amount of Treatment, Mg. Nitrogen	Initial Titer	Preseasonal Titer	Clinical Symptoms	
				Previous	Present
12	0.10	150	600	+++ A	0
5	0.20	3	300	+++	+
2	0.21	3	3	+++ A	+++ A
3	0.21	3	150	+++	++
17	0.24	600	3,000	+++	0
15	0.40	150	1,500	++	+
8	0.49	60	150	+++	+
10	0.54	60	600	+++	+
7	0.57	30	300	+++	0
14	0.61	150	1,500	+++	+
16	0.74	300	6,000	+++	0
13	0.78	150	1,500	+++	+
11	1.27	150	600	+++	0
1	1.52	3	3	+++ A	+++ A
6	1.68	3	300	+++	+

* In this and subsequent tables, the intensity of clinical symptoms of hay fever is expressed by plus signs; 0 denotes no symptoms; +, slight symptoms; ++, symptoms of moderate severity, and +++, frequent or continuous severe symptoms; A denotes asthma in addition to hay fever.

The results shown in table 3 are similar to those in table 2, except that the maximum dose given just before the season, expressed in milligrams of antigen nitrogen, is substituted for the total amount of pollen

injected. This analysis also indicates a scattering of high and low preseasonal titers and of good and poor results of treatment, with no apparent relation to dosage.

It is apparent from these tables that there was no correlation between the amount of antigen that these patients received and either the increase in titer or the clinical result. It may well be, as Rackemann stated, that successful treatment of hay fever depends on optimal dosage for a particular patient. "What this means so far as the underlying mechanism of hay fever is concerned, is a problem, the solving of which must wait upon the collection of data of another kind." [3] Further investigation of the changes in passive transfer titer which follow treatment at various levels of dosage and with different modes of administration may throw further light on this question.

TABLE 3.—*Maximal Dose in Relation to Titer and Clinical Symptoms*

Case No.	Maximal Dose, Mg. Antigen Nitrogen	Initial Titer	Preseasonal Titer	Clinical Symptoms	
				Previous	Present
8	0.02	60	150	+++	+
12	0.02	150	600	+++ A	0
15	0.04	150	1,500	++	+
3	0.05	3	150	+++	++
2	0.06	3	3	+++ A	+++ A
5	0.06	3	300	+++	+
9	0.08	60	300	+++	+++
17	0.10	600	3,000	+++	0
7	0.12	30	300	+++	0
10	0.12	60	600	+++	+
11	0.12	150	600	+++	0
14	0.14	150	1,500	+++	+
16	0.14	300	6,000	+++	0
1	0.16	3	3	+++ A	+++ A
13	0.16	150	1,500	+++	+
6	0.18	3	300	+++	+

Relation of Preseasonal Titer to Clinical Symptoms.—In table 4 the treated patients are divided into three groups according to the intensity of the clinical symptoms experienced during the season under investigation. Although there was overlapping of titers in the three groups, in general the preseasonal titers of the group who had no clinical symptoms were highest and those of the group who had the most severe symptoms (with little or no improvement over previous seasons) were lowest, while those of the group who showed improvement but not complete relief of symptoms were intermediate. The only 2 patients whose titers did not increase were among those who showed no improvement. The percentage of increase in titer was no greater in the group completely relieved than in the intermediate group.

Additional weight is lent to the correlation thus indicated by a tabulation of data on the control patients (table 5). None of these patients

3. Rackemann, F. M.: The Optimal Dosage in the Treatment of Hay Fever, J. Immunol. **11**:91, 1926.

had conspicuous symptomatic improvement over their condition in previous seasons. The preseasonal titers of this group ranged from 3 to 300 units. This range is of the same order as that in the treated group of patients who showed little or no decrease in severity of clinical symptoms.

TABLE 4.—*Relation of Titer to Clinical Symptoms of Treated Patients*

Case No.	Clinical Symptoms		Initial Titer	Preseasonal Titer
	Previous	Present		
16	+++	0	300	6,000
18	+++	0	600	4,500
17	+++	0	600	3,000
12	+++ A	0	150	600
11	+++	0	150	600
7	+++	0	30	300
14	+++	+	150	1,500
13	+++	+	150	1,500
15	++	+	150	1,500
10	+++	+	60	600
6	+++	+	3	300
5	+++	+	3	300
8	+++	+	60	150
4	+++	+	3	150
9	+++	+++	60	300
3	+++	++	3	150
1	+++ A	+++ A	3	3
2	+++ A	+++ A	3	3

TABLE 5.—*Relation of Titer to Clinical Symptoms of Untreated Controls*

Case No.	Clinical Symptoms		Initial Titer	Preseasonal Titer
	Previous	Present		
10	+++	+++	150	300
7	+++	+++	150	150
6	++	+++	30	60
8	+++	++	150	60
4	++	+++	30	30
5	+++	++	30	30
1	±	+	3	3
9	0	0	150	300
3	0	0	30	30
2	0	0	3	3

The 3 patients who exhibited no clinical evidence of hay fever showed titers of the same range, both in the original and in the preseasonal titrations, as did the patients with manifest hay fever. This supports the generally accepted conception that the presence of passive transfer antibody within the range of titer shown by patients with manifest allergic conditions is not the only factor necessary to establish clinical hypersensitiveness.

Intracutaneous Tests.—Intracutaneous tests with pollen extracts containing 0.001 and 0.01 mg. of nitrogen per cubic centimeter, respectively, were done on both treated and control patients after blood was with-

drawn for each titration. In each case the smallest amount of antigen necessary to produce a wheal about 2 mm. in diameter was injected intracutaneously on the outer surface of the upper part of the arm. In fifteen minutes the reaction was read, and the diameters of the wheal and the erythema, and the presence or absence of pseudopods were recorded.

During the period between the original and the preseasonal titrations, the cutaneous reactions of the treated group showed a general tendency to decrease, while those of the control group remained relatively constant. The reduction in the size of the cutaneous reactions was by no means consistent in all treated patients, nor did it appear to be directly related to antibody titer or to clinical results of treatment. No significant changes were noted during the subsequent periods of testing.

COMMENT

The series of observations reported here is the first, to our knowledge, which included data on untreated controls and in which serial titrations were taken on treated and untreated patients at similar periods with relation to treatment and the season of pollination. The method of titration employed is believed to have considerable accuracy, since each titration was performed in triplicate and results which checked to within 1 titration level were obtained.

The evidence presented indicates that the passive transfer antibody titer is relatively constant over a period of several months in the absence of injection of pollen extracts or of contact with air-borne pollen. The rise of titer in 16 of 18 treated patients, as contrasted with the lack of increase in controls, appears to establish a direct relation between the injection of pollen extracts and a rise of titer.

High preseasonal titers were noted among the patients who had the maximal protection against clinical symptoms of hay fever and low titers among those who had little or no protection. This observation suggests that when the usual doses are given, excluding massive doses, the mechanism of protection following injection of pollen extracts may be in the nature of an acquired immunity. Similar changes in titer and a similar relation between increase in titer and relative freedom from symptoms was observed in a small group of children sensitive to foods.[4] This change in titer, however, is only one factor; other important factors may be involved. Furthermore, in some cases the effect of an increase in titer may be concealed by factors which are not recognized.

4. Lippard, V. W., and Schmidt, W. M.: Human Passive Transfer Antibody: IV. Studies on Children Hypersensitive to Foods, Am. J. Dis. Child., to be published.

Normal persons have no detectable passive transfer antibody. Therefore, the optimal state would seem to be one in which none of the antibody is present. In the presence of hypersensitiveness, however, a state of protection from symptoms appears to be closely related to the presence of antibody adequate to neutralize absorbed antigen before it reaches the tissues.

The mechanism whereby patients suffering from hay fever are afforded protection has been a subject of discussion since the institution of pollen therapy. The conception prevalent before the demonstration of passive transfer antibodies was that antibody-like substances were confined to the sensitive tissues and that the alleviating effect of specific treatment was dependent on exhaustion of tissue antibodies, i. e., on desensitization.[5]

In 1926 Levine and Coca [6] reported on a group of patients with hay fever in whom the reagins [7] were titrated by the methods of serum dilution and antigen dilution before and after a course of treatment. No untreated control patients were included in the group. It was found that 10 patients showed no change in reagin content, while 9 showed a definite increase. Because the group in whom the titer increased exhibited the same average degree of protection from symptoms as the group who showed no increase in titer, it was concluded that quantitative changes in reagin titer provide no basis for an explanation of the alleviating effect of specific therapy. The evidence was accepted as indicating, however, that the alleviating effect of therapy is not dependent on desensitization.

Previously reported observations [1] provide evidence that the method of serum dilution, while serving to distinguish between serums of very high and very low titer, fails to differentiate between serums in the middle ranges of antibody potency. It may therefore be suggested that the method employed by these investigators revealed only the most marked increases of antibody titer, while moderate increases were not revealed.

The report of Baldwin and Glaser [8] throws additional light on this subject. Of 8 patients studied by dilution titrations before and after

5. Cooke, R. A.; Flood, E. P., and Coca, A. F.: Hay Fever: The Nature of the Process and of the Mechanism of the Alleviating Effect of Specific Treatment, J. Immunol. **2**:217, 1917. Rackemann, F. M.: The Mechanism of Hay Fever, Arch. Int. Med. **30**:221 (Aug.) 1922.

6. Levine, P., and Coca, A. F.: Specific Treatment of Hay Fever: Nature of the Alleviating Effect, J. Immunol. **11**:449, 1926.

7. The terms "atopic reagin," as employed by Coca and others, and "idioceptor," as used by Harley, are synonymous with "passive transfer antibody."

8. Baldwin, L. B., and Glaser, J.: Effect of Treatment on the Skin and Mucous Membrane Sensitivity and on Reagins in Hay Fever, J. Allergy **8**:129, 1937.

treatment, 5 who had good clinical results showed a rise in titer. One patient, who had the poorest clinical result, showed no rise and the lowest titer. Two other patients also showed no increase in titer, but they had moderately good clinical results. Of these, 1 showed a relatively high titer before treatment. Therefore, only 1 patient of this group of 8 may be considered exceptional to the concept that a high preseasonal titer and protection from symptoms are associated phenomena.

The experiments of Cooke and his associates,[9] reported in 1935, which were based on titrations on 8 patients before and after treatment, depended on the employment of both the dilution and the neutralization method of titration. No untreated controls were reported on. Titrations with a neutralization method revealed a rise in titer in all cases, while the dilution method revealed a rise in 3, equality in 4 and a slight decrease in 1. Harley[10] also reported incomplete parallelism in results when the two methods of titration were applied to pretreatment and post-treatment serums. These authors postulated a separate factor, which they termed "inhibiting substance."

In the reports cited, as in the present one, the patients were treated with moderate doses of antigen. When massive doses are administered, the mechanism of protection may be different. Recently Urbach[11] advanced the hypothesis that there may be two mechanisms, one dependent on an increase in antibody titer and the other on a decrease or loss. This hypothesis would explain the results of Harley,[12] who after using the dilution method of titration reported a decrease in antibody titer following frequent administration of massive doses of pollen extracts.

SUMMARY AND CONCLUSIONS

Twenty-five patients with hay fever and 3 hypersensitive persons with no history of hay fever, but with passive transfer antibody for ragweed or timothy were studied over twelve to eighteen months. Eighteen were treated by injection of pollen extracts, and 10 comprised an untreated control group. Four serial titrations of passive transfer antibody were performed on each patient in both groups at similar

9. Cooke, R. A.; Barnard, J. H.; Hebald, S., and Stull, A.: Serologic Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever), J. Exper. Med. **62**:733, 1935.

10. Harley, D.: Hay Fever—The Effect of Pollen Therapy on the Skin Reactions: II. A Reaction-Inhibiting Substance in the Serum of Treated Patients, J. Path. & Bact. **44**:589, 1937.

11. Urbach, E.: Deallergisierung oder Desensibilisierung als Grundlage der antiallergischen Therapie? Wien. klin. Wchnschr. **48**:277, 1935.

12. Harley, D.: Hay Fever: The Mechanism of Specific Desensitization, Lancet **2**:1469, 1933.

periods in relation to season of pollination. The method of titration was based on the neutralization of antibody by specific antigen.

1. A series of injections of pollen extracts is followed by an increase in titer of passive transfer antibody. This observation was recorded for 16 of 18 patients.

2. The passive transfer antibody titer remains relatively constant over a period of months in the absence of injection of pollen extracts or exposure to air-borne pollen. The titers of untreated patients increase slightly, however, during periods of exposure to pollen.

3. In the group studied, an increase in titer of passive transfer antibody is associated with relief from clinical symptoms of hay fever. Only 1 patient who showed a significant increase in titer was not relieved.

4. There is no correlation between the amount of antigen injected and either increase in titer or therapeutic effect.

525 East Sixty-Eighth Street.

MINIMAL VITAMIN C REQUIREMENTS OF ARTIFICIALLY FED INFANTS

A STUDY OF FOUR HUNDRED AND TWENTY-SEVEN CHILDREN UNDER A CONTROLLED DIETARY REGIMEN

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DETROIT

The lack of extensive material concerning the minimal requirement of vitamin C necessary to prevent scurvy in infants has frequently handicapped research workers. Information indicating the amount of vitamin C required by the average healthy infant under usual conditions in the home has been inadequate. While a survey made in the homes entails a great deal of added effort and is impossible to control rigidly, the results are applicable directly to the problem of infant management. The deficiency in control and supervision without hospitalization is more than offset by the natural environment. The infinitely greater number of infants are subjected to ordinary home surroundings, both psychologic and physical. It is this larger group which must attract the interest of physicians, for as the group is larger so is the opportunity of service greater.

A detailed study of a cross section of Detroit's infants of indigent or near-indigent parents has been made through the resources of the Children's Fund of Michigan and the Children's Hospital of Michigan. Four hundred and twenty-seven babies were studied until they were 1 year of age; 80 per cent of these were examined periodically for nine

From the Research Laboratory, Children's Fund of Michigan and the Children's Hospital of Michigan.

The infants were obtained through the Detroit Department of Health, Harper Hospital, Florence Crittenton Hospital, Woman's Hospital and private physicians in Detroit.

Senia Kangas, R.N., director of nursing service; Rachel Moore, roentgen technician; Betty Munday, M.A., Louise Emerson, A.B., and Marion L. Shepherd, A.B., laboratory technicians; Francis Slyker, Ph.B., statistician, and Helen R. Sternberger, Ph.D., who made the analyses of vitamin C, assisted in this study.

months or longer. The results indicate the minimal dose of ascorbic acid necessary to prevent scurvy in the healthy infant; they point to infection as a predisposing factor in the development of scurvy. The findings suggest that so-called latent scurvy is actually mild scurvy. Loss of vitamin C by deterioration and the effect of the concentration of vitamin C in systemic deficiencies must be considered in prophylaxis. An important distinction can be made between the amount of vitamin C ingested and the amount assimilated. The assimilation cannot be measured.

Seven infants who did not receive vitamin C except in evaporated milk were observed in a supplemental study. The deficiency became known when they were several months old, and they were subsequently subjected to closer supervision and were given orange juice or lemon powder. Since the classic investigation of Holst and Frölich [1] it has been generally recognized that scurvy is the same disease in all of the susceptible organisms. It has the same etiology, the same unknown pathogenesis, a similar syndrome and identical therapeutics.[2] Höjer [2] has pointed out that scurvy is a disease of growth and therefore a "central pediatric problem." The history and modern concepts concerning the aspects of vitamin C and infantile scurvy have been summarized recently by outstanding investigators in this field of research.[3]

Vitamin C, essential to normal development, is easily destroyed, especially by exposure to air and heating, and the extensive losses occurring through cooking have been accurately reported.[4]

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1. Holst, A., and Frölich, T.: Experimental Studies Relating to "Ship Beri-Beri" and Scurvy, J. Hyg. **7**:634, 1907.

2. Höjer, J. A.: Studies in Scurvy, Acta pædiat. (supp.) **3**:8, 1924.

3. (*a*) Hess, A. F.: Scurvy, Past and Present, Philadelphia, J. B. Lippincott Company, 1920. (*b*) Still, G. F.: Infantile Scurvy, Arch. Dis. Childhood **10**: 210, 1935. (*c*) Eddy, W. H., and Dalldorf, G.: The Avitaminoses, Baltimore, Williams & Wilkins Company, 1937. (*d*) King, C. G.: Vitamin C, Ascorbic Acid, Physiol. Rev. **16**:238, 1936. (*e*) Hess, A. F.: Recent Advances in Knowledge of Scurvy and the Antiscorbutic Vitamin, J. A. M. A. **98**:1429 (April 23) 1932. (*f*) McIntosh, R.: Infantile Scurvy, Barlow's Disease, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, chap. 35.

4. King.[3d] McIntosh.[3f] Chick, H., and Dalyell, E. J.: The Influence of Overcooking Vegetables in Causing Scurvy Among Children, Brit. M. J. **2**:546, 1920. Tressler, D. K.; Mack, G. L., and King, C. G.: Factors Influencing Vitamin C Content of Vegetables, Am. J. Pub. Health **26**:905, 1936. Sherman, H. C., and Smith, S. L.: The Vitamins, New York, The Chemical Catalog Company, Inc., 1931. McCollum, E. V., and Simmonds, N.: The Newer Knowledge of Nutrition, New York, The Macmillan Company, 1925. Plimmer, R. H. A., and Plimmer, V. G.: Food, Health and Vitamins, London, Longmans, Green & Co., 1929. Fenton, F.; Tressler, D. K., and King, C. G.: Losses of Vitamin C During the Cooking of Peas, J. Nutrition **12**:285, 1936.

Study of the chemical characteristics of vitamin C has resulted in extensive knowledge regarding the distribution of the vitamin in the tissues of plants and animals. King [3d] has summarized the investigations on the physiologic function of the vitamin, in relation first to specific enzymes, second to its distribution and function in plants and third to its distribution and function in animal tissues. In relation to specific enzymes, it is difficult to state whether the changes in tissues observed as a result of vitamin C deficiency are due directly to the absence of the vitamin from the tissue cells or are due to the physiologic disturbances caused by lowered production of enzymes in interrelated functions of the tissues, as an indirect consequence of the absence or deficiency of the vitamin. King stated that ascorbic acid is fundamentally important in tissue respiration, the vitamin acting as a hydrogen-transporting agent between organic metabolites and, indirectly, molecular oxygen.

Ascorbic acid is formed rapidly in sprouting seeds, and it apparently reaches a high concentration in all rapidly growing stem or root tips, green leaves, seeds and pods. Its occurrence in relatively high concentration in the glandular tissues, in which metabolism is highest, is evidence of an essential metabolic role.

The two specific physiologic roles which seem to be established for vitamin C in animal tissues are the respiratory function, similar to that demonstrated in relation to plant life, and the regulation of the colloidal condition of intercellular substance, as shown by Wolbach and associates,[5] an effect described by Höjer [2] as "a general insufficiency in the collagen formation." Most of the gross effects of severe scurvy can be reasonably well explained on the basis of these two functions.

According to the published experimental findings,[3d] there is no evidence of serious loss of vitamin C during the process of assimilation from the digestive tract, the excessive vitamin C of the diet being rapidly excreted without damage to the kidneys. When a diet containing no vitamin C is given, excretion in the urine continues, and the body tissues are markedly depleted before there is any external indication of scurvy. The quantity of the vitamin utilized in metabolic processes can be only approximately estimated from the data thus far available.

The quantitative vitamin C requirement of human beings and the physiologic and pathologic factors affecting it remain an enigma, though there have been many recent studies and approaches to the problem.

5. (*a*) Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, Arch. Path. **1**:1 (Jan.) 1926. (*b*) Menkin, V.; Wolbach, S. B., and Menkin, W. F.: Formation of Intercellular Substance by Administration of Ascorbic Acid (Vitamin C) in Experimental Scorbutus, Am. J. Path. **10**:569, 1934.

Brennemann [6] in 1913 drew attention to the clinical use of undiluted whole milk, boiled for five minutes, in the rarely occurring cases of infantile scurvy. He reported good results from its use and emphasized "that scurvy occurs only in children with a predisposition to the disease." In 1923 the same author declared: "The amount of vitamin necessary to afford ample protection in the human is quite uncertain, is apparently a small one, is drawn from many sources and the individual factor may play a larger part than we now know." [7]

From her studies on infants in Vienna, Austria, Chick [8] reported that 4 to 10 cc. of fresh lemon juice is a prophylactic daily dose for infants. Gerstenberger [9] was able to cure a scorbutic infant with a daily dose of spray-dried orange juice equivalent to 45 cc. of the fresh juice. In addition, this investigator demonstrated that an amount of spray-dried fresh lemon juice equal to 20 cc. of lemon juice per liter of milk had antiscorbutic potency sufficient to cure the disease in 6 scorbutic infants, as determined by clinical and roentgen findings—results which were later corroborated by Martin.[10]

Since the isolation and identification of vitamin C [11] it has been possible to make more accurate determinations of the vitamin C requirement of human beings. Using the antiscorbutic value of human milk as the criterion for the quantitative needs of the normal infant, King and Selleg [12] were able to augment the vitamin C content of breast milk by an increase in the vitamin C content of the diet. They stated: "It seems evident that the normal requirement of vitamin C per day for an infant may be estimated from the amount supplied in mother's milk when the parent is receiving a good diet."

Whitnah and Riddell [13] stressed the value of fresh cow's milk as an important source of vitamin C. If a quart (946 cc.) of fresh milk

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6. Brennemann, J.: Boiled Versus Raw Milk: An Experimental Study of Milk Coagulation in the Stomach, Together with Clinical Observations on the Use of Raw and Boiled Milk, J. A. M. A. **60**:575 (Feb. 22) 1913.

7. Brennemann, J.: Vitamins and the Baby, J. Michigan M. Soc. **22**:519, 1923.

8. Chick, H.; Dalyell, E. J.; Hume, M.; MacKay, H. M., and Smith, H. H.: The Aetiology of Rickets in Infants, Lancet **2**:7, 1922.

9. Gerstenberger, H. J.; Smith, D. M., and Hacker, G. L.: Observations on Effect of Aging on the Potency of Spray-Dried Antiscorbutic Material, J. Pediat. **3**:93, 1933.

10. Martin, C. W.: Some Dried Foods Used in Infant Feeding, New York State J. Med. **32**:1012, 1932.

11. (*a*) King.[3d] (*b*) Zilva, S. S.: The Isolation and Identification of Vitamin C, Arch. Dis. Childhood **10**:253, 1935. (*c*) Macy, I. G.: The Nutritive Aspects of Human Milk, Yale J. Biol. & Med. **4**:451, 1932.

12. King, C. G., and Selleg, I.: The Vitamin C Content of Human Milk and Its Variation with Diet, J. Nutrition **11**:599, 1936.

13. Whitnah, C. H., and Riddell, W. H.: Milk as a Source of Vitamin C, Science **83**:162, 1936.

were consumed per day, the results would corroborate the findings of Göthlin,[14] who deduced from the measure of capillary resistance in a large number of school children and adults of the Nordic race that the minimum antiscorbutic protective dose is from 0.7 to 1 cc. of orange juice per kilogram of body weight or from 19 to 27 mg. of vitamin C daily. Widenbauer[15] estimated the daily dose of antiscorbutic vitamin necessary to artificially fed infants as 6 mg. per kilogram. With oral doses of 20 to 40 mg. of ascorbic acid Abt and Epstein[16] cured advanced scurvy in 3 infants, aged 9 to 12 months, in eight to twenty-one days. They reported the oral doses used by various persons to be from 30 to 60 mg. daily for treatment of infants 10 to 15 months of age and cited its use by Kramer in a daily prophylactic dose of 15 to 50 mg. for premature, newborn and older healthy nurslings. They further stated that 10 mg. of crystalline ascorbic acid corresponds approximately to 30 cc. of the active vitamin C of fresh orange juice in antiscorbutic potency.

From a study of the urinary excretion of ascorbic acid and its concentration in the blood in cases of infantile scurvy, Ingalls[17] found an absolute depletion of ascorbic acid in the urine and exceedingly low values in the plasma. Replenishment of this vitamin depended primarily on the dose of ascorbic acid employed. This author aptly stated:

> It would seem logical to suppose that saturation is the truly optimal state of ascorbic acid nutrition for the infant, since in the event of an increased demand or decreased supply, the vitamin depot is presumably larger than in partial saturation. However, it is certainly true also that normal health can be maintained at a lower level of supply. Further study is required to define more precisely the minimal protective doses for human beings.

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14. (*a*) Göthlin, G. F.: A Method of Establishing the Vitamin C Standard and Requirements of Physically Healthy Individuals by Testing the Strength of Their Cutaneous Capillaries, Skandinav. Arch. f. Physiol. **61**:225, 1931; (*b*) Methode zur Bestimmung der Festigkeit der Hautcapillaren and zu indirekter Beurteilung des individuellen C-Vitaminstandards, Klin. Wchnschr. **11**:1469, 1932; (*c*) Outline of Method for Determination of the Strength of Skin Capillaries and the Indirect Estimation of Individual Vitamin C Standard, J. Lab. & Clin. Med. **18**:484, 1933. (*d*) Göthlin, G. F.; Frisell, E., and Rundquist, N.: Experimental Determinations of the Indispensable Requirements of Vitamin C (Ascorbic Acid) of the Physically Healthy Adult, Acta med. Scandinav. **92**:1, 1937.

15. Widenbauer, F.: Ascorbinsäurestudien an Säuglingen, Klin. Wchnschr. **15**: 815, 1936.

16. Abt, A. F., and Epstein, I. M.: Cevitamic Acid (Ascorbic Acid) in Treatment of Infantile Scurvy, J. A. M. A. **104**:634 (Feb. 23) 1935.

17. Ingalls, T. H.: Studies on the Urinary Excretion and Blood Concentration of Ascorbic Acid in Infantile Scurvy, J. Pediat. **10**:577, 1937.

Since there are serious limitations to the clinical use of both the urinary excretion of ascorbic acid [18] and its concentration in the blood,[17] for the diagnosis of subclinical vitamin C deficiency other diagnostic methods must be sought.

Opinions vary as to the effect of different pathologic conditions on the onset of scurvy. Interpretations differ as to whether the deleterious effects observed are due to excessive loss from the body tissues, as in infections,[19] to the oxidizing effect of abnormal products in the intestinal canal on the antiscorbutic substance before its absorption,[1] or to the rapid and marked depletion of the vitamin from the glandular tissue.[3d] The relation of a diet containing vitamin C to formation of blood,[20] to blood coagulation time [21] and to capillary resistance [22] in mild and in manifest scurvy should be investigated further.

In a series of studies on the growth and development of infants, it was essential to supply an adequate amount of vitamin C in the diets while determining the plane of health during the first year of life; knowledge of any scurvy present at this time was necessary. The analysis of the data collected in these general studies on growth clarifies some of the controversial points as to the amount of ascorbic acid necessary to maximum efficiency of bodily function and as to the indefinite condition formerly referred to as latent scurvy.

PROCEDURE

The average age of the 427 infants in the primary study at the beginning of observation was 5½ weeks. Ages at which the first and last examinations were made are tabulated below. Approximately 80 per cent of the subjects were seen over a period of nine months or more.

Age of Infants at First and at Final Observation

Age in days at first observation	0-6	7-13	14-27	28-41	42-55	56-83	84 or More	Total
Number of infants	1	1	97	134	100	86	8	427

Age in days at last observation	2-92	93-183	184-274	275-365	366-456	457 or More	Total
Number of infants	13	26	44	245	98	1	427

18. Ingalls.[17] Hawley, E. E.; Stephens, D. J., and Anderson, G.: The Excretion of Vitamin C in Normal Individuals Following a Comparable Quantitative Administration in the Form of Orange Juice, Cevitamic Acid by Mouth and Cevitamic Acid Intravenously, J. Nutrition **11**:135, 1936.

19. Holst and Frölich.[1] Ingalls.[17]

20. Mettier, S. R.; Minot, G. R., and Townsend, W. C.: Scurvy in Adults. Especially the Effect of Food Rich in Vitamin C on Blood Formation, J. A. M. A. **95**:1089 (Oct. 11) 1930. Parsons, L. G., and Smallwood, W. C.: Studies in Anemia of Infancy and Early Childhood: Anemia of Infantile Scurvy, Arch. Dis. Childhood **10**:327, 1935.

21. Presnell, A. K.: Relation of Avitaminosis C to Blood Clotting, J. Nutrition **8**:69, 1934.

22. Greene, D.: Evaluation of the Capillary Resistance Test in the Diagnosis of Subclinical Scurvy, J. A. M. A. **103**:4 (July 7) 1934.

Monthly, and in some cases bimonthly, examinations and anthropometric measurements were made in the special growth clinic of the Children's Fund of Michigan and the Children's Hospital of Michigan.

The diets were as rigidly controlled as possible. Two visiting nurses from the clinic kept the mothers supplied with the essential materials for the formulas and supervised the care of the infants in their own homes. The mothers kept daily records of the consumption of food, and histories of the intervening periods were taken at each visit to the clinic. Information relative to the prenatal and natal factors which might possibly have influenced the nutrition, growth and development of the infant was obtained as a part of the initial record for each case.

Three technicians of the laboratory staff made determinations of hemoglobin content and red cell counts at each visit to the clinic. White blood counts and cover slip smears for differential study were made for each infant at the initial visit and thereafter as indicated. Determinations of hemoglobin were done on the blood of each mother at the time of the first visit, and if the reading was 10 Gm. per hundred cubic centimeters or below a follow-up study was done.

Separate roentgen exposures of the left arm, left leg, left wrist and left foot of each infant were made at the time of the first visit. These were repeated at the approximate ages of 4 months, 6 months, 9 months and 12 months, and either full sets of roentgenograms or exposures of the left hand and wrist were made at other monthly visits to the clinic. A total of 10,342 exposures were made of the 434 children, an average of more than 23 each. The roentgenograms were studied by trained observers,[23] who used the criteria of Park and his associates[24] for the occurrence of rickets, scurvy[25] and mineralization.

The capillary resistance test (Göthlin's method[26]) was made on 112 of the 427 infants between the ages of 4½ months and 8 months.[27]

Psychometric developmental examinations[28] were made of 69 infants at the ages of 6 months, 9 months and 12 months. An additional 58 infants had 1 psychometric test at the age of 12 months.[29]

The basal formula for all the infants was a mixture of evaporated milk, water and corn syrup. The formula was acidified by the addition of commercial

23. All of the roentgenograms were read in group conferences or individually by each of us.

24. Park, E. A.; Guild, H. G.; Jackson, D., and Bond, M.: The Recognition of Scurvy with Especial Reference to the Early X-Ray Changes, Arch. Dis. Childhood **10**:265, 1935.

25. Cooley, T. B., and Reynolds, L. W.: The Interpretation of X-Ray Films in Diagnosis of Rickets, J. Pediat. **10**:743, 1937.

26. Göthlin and others.[14] Greene.[22]

27. Margaret K. Patterson, M.D., and Dorothy Snell, M.D., of the Children's Hospital of Michigan, made the capillary resistance tests.

28. Martha G. Colby, Ph.D., and her staff from the Psychology Department of the University of Michigan made all the psychometric developmental examinations of the infants.

29. Colby, M. G.; Macy, I. G.; Poole, M. W.; Hamil, B. M., and Cooley, T. B.: Relation of Increased Vitamin B (B_1) Intake to Mental and Physical Growth of Infants, Am. J. Dis. Child. **54**:750 (Oct.) 1937.

dehydrated lemon juice of known ascorbic acid content.[30] This was added in standard amounts (11.6 Gm. to the twenty-four hour formula) to supply the normal requirement of the infants. Table 1 shows the distribution of the 427 infants in the different groups and the dietary supplements that were given daily.[31]

An attempt was made to increase the consumption of milk after the age of 8 weeks by using less water in the formula and by planning to have the day's formula contain 1 can of evaporated milk (approximately 13½ ounces [399 cc.] by volume) by the time the infant reached the age of 3½ months. For uniformity, this level of milk was maintained thereafter.

Vitamin C Supplement.—An intense effort was made to obtain uniformity in the diets of all of the infants in regard to certain basic foods and accessory nutrients, with particular attention to the vitamins. Powdered lemon juice was selected as the medium for the vitamin C

TABLE 1.— *Dietary Supplements Given the Various Groups of Infants*

Group	No. of Infants	Total Available* Vitamin C		Average Daily Dietary Supplements		
		Mg.	International Units	Vitamin D U. S. P. Units	Vitamin B_1 Sherman-Chase Units	Other Additions†
B-1	76	10.25	2,050	95-162 (Irrad. milk)	250	
C-1	57	9.85	1,970	.....	150	
B-2	66	10.25	2,050	250-600 (CLO)	250	
C-2	51	9.85	1,970	675 (CLO)	150	
V-1	60	9.85	1,970	810 (CLO)	186	Strained vegetable soup
V-2	78	9.85	1,970	250-600 (CLO)	186	Strained vegetable soup
P-T	13	9.85	1,970	250-600 (CLO)	186	Strained vegetable soup
C-3	26	9.85	1,970	250-600 (CLO)	150	
Total	427					

* The quantity of vitamin C available was determined by considering the results of titrations of the twenty-four hour formulas (tables 2 and 3).

† Poole, M. W.; Hamil, B. M.; Cooley, T. B., and Macy, I. G.: Addition of Vegetable Soup and Strained Vegetables to Diet of Artificially Fed Infants, Am. J. Dis. Child. **55**:1158 (June) 1938.

supplement[32] because it contains less lipochrome substance than the orange concentrate. The amount to be used was decided by a process

30. The powdered lemon juice was furnished by the Borden Company, New York, through Mr. Louis J. Auerbacher. The titration values of vitamin C showed that this powder contains from 0.81 to 0.89 mg. of vitamin C per gram. The vitamin B_1 content of the lemon powder, as determined by G. C. Supplee, Ph.D., of the Dry Milk Company, is 13 Sherman-Chase units per gram of solid.

31. The infants in groups V-1 and C-2 were being observed in a special study conducted by the United States Children's Bureau. Martha M. Eliot, M.D., Donald J. Barnes, M.D., and Florence Browne, M.D., cooperated in this study.

32. Holt, L. E.: Symposium on Vitamins, New York M. J. **113**:305, 1921. Barenberg, L. H.; Abramson, H., and Messer, W. H.: Five Years' Clinical Experience with Lemon Juice-Milk, Am. J. Dis. Child **39**:948 (May) 1930. Gonce, J. E., Jr., and Templeton, H. L.: Citric Acid Milk in Infant Feeding, ibid. **39**: 265 (Feb.) 1930.

of deduction. Givens and McClugage [33] and Givens and Macy [34] showed that 1 Gm. of lemon or orange powder has the vitamin C potency of 3 cc. of fresh juice.

As to the satisfactory antiscorbutic intake, medical opinion as expressed in the literature varies greatly, ranging from an estimation of 10 to 20 cc. of fresh lemon juice per day to one of 19 to 50 mg.[35] of ascorbic acid per day. It was concluded that 2 teaspoonfuls (5.8 Gm.) of powdered lemon juice was adequate as a prophylactic dose for infants to the age of 8 to 12 weeks. Thereafter the intake was doubled. This intake of supplementary ascorbic acid would approximate that usually given in pediatric practice. The powdered lemon juice also fulfilled the practical need for an antiscorbutic material of small bulk, uniform potency, digestibility and tolerance which could be used by the mother without inconvenience or requirement of great intelligence and would afford economical distribution.

During the course of the study, titration values were ascertained on numerous shipments of the lemon powder used.[36] The average vitamin C value of the powder at the time the cans were opened was found to be 0.84 mg. per gram. During the ten days to two weeks necessary to use one 4 ounce (118 cc.) can the depreciation in vitamin C content was approximately 0.05 mg. per gram. While this deterioration showed that the infants were receiving less vitamin C than had been planned, the difference was slight, and the absence of clinical evidence of deficiency at the monthly examinations caused us to continue the doses as originally planned.

It is customary to prepare infant formulas in sufficient quantities to last throughout the twenty-four hour period. It was therefore important to determine whether retention in the refrigerator produced loss in the vitamin C content. It is well known that vitamin C is readily oxidized. To compute the actual amount of ascorbic acid consumed daily by the infants, the various modified formulas were titrated at various feeding intervals throughout the twenty-four hour period. The results of observations on the progressive loss in the ascorbic acid content of the formulas are given in table 2.

33. Givens, M. H., and McClugage, H. B.: The Antiscorbutic Property of Fruits: I. An Experimental Study of Dried Orange Juice, Am. J. Dis. Child. **18**:30 (July) 1919.

34. Givens, M. H., and Macy, I. G.: The Antiscorbutic Property of Some Desiccated Fruit Juices, J. Biol. Chem. **46**:xi, 1921.

35. Eddy and Dalldorf.[3c] Menkin and others.[5b] Brennemann.[6, 7] Chick and others.[8] Gerstenberger and others.[9] Martin.[10] Zilva.[11b] Macy.[11c] King and Selleg.[12] Whitnah.[13] Göthlin.[14a]

36. Poole, M. W.; Hamil, B. M.; Cooley, T. B., and Macy, I. G.: The Stabilizing Effect of Increased Vitamin B Intake upon the Growth and Nutrition of Infants, Am. J. Dis. Child. **54**:726 (Oct.) 1937.

To determine whether any of the loss of vitamin C could be ascribed to the presence of any of the other ingredients of the formula, several test formulas were titrated. The results are given in table 3.

TABLE 2.—*Titration Value of Vitamin C in Formulas*

Formula Mixtures	Vitamin C Value of Formula		Loss of Vitamin C	
	Immediately After Mixing, Mg. per Oz.	After 24 Hours' Refrigeration, Mg. per Oz.	After 24 Hours' Refrigeration, per Cent	Average Loss Before Feeding, per Cent
Plain evaporated milk, dilute*	0.336	0.188	44	25
Plain evaporated milk, concentrated†	0.460	0.360	22	17
Vegetable added, dilute*	0.308	0.174	44	25
Vegetable added, concentrated†	0.458	0.287	35	21
Evaporated milk with vitamin B_1, dilute*	0.289	0.131	54	33
Evaporated milk with vitamin B_1, concentrated†	0.464	0.235	49	27

* Dilute formula: 8 ounces (238 cc.) evaporated milk, 16 ounces (473 cc.) water, 3 tablespoons Karo, 2 teaspoons lemon powder.

† Concentrated formula: 13 ounces (384 cc.) evaporated milk, 16 ounces water, 3 tablespoons Karo, 4 teaspoons lemon powder.

TABLE 3.—*Losses of Vitamin C Content in Test Solutions Determined by Titration*

Formula Mixtures	Vitamin C Value of Formula		Vitamin C Loss After 24 Hours' Refrigeration, per Cent
	Immediately After Mixing, Mg. per Oz.	After 24 Hours' Refrigeration, Mg. per Oz.	
Dilute control with ascorbic acid and citric acid to give usual acidity, with Karo	0.282	0.160	43
Dilute control with ascorbic acid and citric acid to give usual acidity, without Karo	0.286	0.179	38
Lemon powder in water, dilute*	0.215	0.147	31
Lemon powder in water, concentrated†	0.355	0.237	33
Milk properly diluted with citric acid to give usual acidity, plain evaporated, concentrated†	0.089	0.055	38
Milk properly diluted with citric acid to give usual acidity, plain evaported, dilute*	0.137	0.062	55
B_1 milk, dilute*	0.104	0.061	41
B_1 milk, concentrated†	0.137	0.094	31

Vitamin C Value of the Milk‡	Evaporated Milk	
	Mg. per Cc.	Mg. per 13½ Oz. Can
Vitamin C in plain evaporated milk	0.0088	3.564
Vitamin C in B_1 milk (prepared in summer)	0.0106	4.293
Vitamin C in B_1 milk (prepared in winter)	0.0098	3.969

* See footnote *, table 2.

† See footnote †, table 2.

‡ These figures represent the average of two cans from each lot of milk.

RESULTS

Examination of the monthly roentgenograms for evidence of rickets and for the usual criteria of scurvy revealed no scurvy among the 427 infants known to receive the prescribed quantity of powdered

lemon juice. It was known that 7 additional infants had not received vitamin C beyond that contained in the evaporated milk. One infant in an advanced state of scurvy with marked subperiosteal hemorrhages had just recovered from a severe attack of bronchopneumonia when the grandmother admitted that the mother had never given the baby any of the antiscorbutic material supplied. The other 6 infants did not receive any additional vitamin C until the ages shown in table 4. A diagnosis of mild scurvy in 2 of these was made by Park's criteria; however, in 1 case the diagnosis is doubtful, being made from only one set of roentgenograms. Table 4, because of the small number of cases presented, is not intended to be conclusive, but some interesting inferences may be made.

TABLE 4.—*Data on Seven Infants Who Did Not Receive Vitamin C Adjuvant at an Early Age*

		Age in Days										
					Diagnosis of Scurvy		Hemoglobin Below 10 Gm.			Infections		Average Milk Intake per Day,* Ounces
Case No.	Date of Birth	First Observation	Vitamin C Added	Discharge	Slight	Clinical		Rate of Growth	Prenatal History	No.	Severity	
435	3/18	24	167	216	...	...	....	Slow	Good	2	Slight	11.5
452	3/25	11	...	138	98	...	....	Slow	Poor	1	Moderate	10.0
465	3/26	42	224	224	...	...	....	Moderate	Good	3	Slight	12.9
467	12/12	30	224	315	176	224	....	Slow	Fair	2 1	Slight Severe	11.3
483	3/31	54	168	203	...	...	77 and 133	Slow	Good	3 1	Slight Severe	13.0
497	3/31	19	126	196	...	...	61-112†	Slow	Poor to fair	5	Slight	11.2
506	3/24	42	...	226	61-191†	...	....	Rapid	Good	2	Slight	12.5

* Approximately 0.20 mg. of vitamin C is available per ounce (30 cc.) of evaporated milk.
† Similar observations were recorded at intervening visits. Conditions in the home were good in all cases.

The work of Roberts and others [37] showed decided variation in results of capillary resistance tests; these results were not related to infections but showed distinct parallelism to the amount of vitamin C in the diet and the amount of vitamin D available from sunlight. In these 7 cases it is possible that considerable seasonal effect is represented. Six of these babies were seen during the period of maximal seasonal effect, whereas the 427 babies in the primary study were seen throughout a longer period, and study was started on them at varying seasons.

All of the 10,342 roentgenograms were examined for the minute changes described by Park and others [24] from their correlation of roentgen with histologic observations. These examinations were conducted either individually or in group conference.

37. Roberts, L. J.; Blair, R., and Bailey, M.: Seasonal Variations in Capillary Resistance of Institution Children, J. Pediat. **11**:626, 1937.

TABLE 5.—*Analysis of Vital Phenomena Related to Subclinical Scurvy* *

	1933-1934											1934-1935								1935-1936			
Case numbers	4	5	16	17	19	38	39	70	87	100	108	136	156	191	253	254	258	262	265	343	372	Total	New
Scurvy on roentgen study:																							
Before 6 months of age	x	..	..	x	x	x	x	..	..	..	..	..	..	..	x	x	..	..	..	x	..	8	8
Before 8 months of age	x	x	x	..	..	x	..	..	..	..	..	x	x	..	x	..	..	x	x	x	..	10	6
Before 12 months of age	..	..	x	..	..	..	..	x	x	x	x	x	..	x	..	..	x	x	x	..	x	11	7
Daily vitamin C consumed:																							
More than 9 mg	..	x	..	..	..	x	..	..	x	x	..	x	x	x	x	x	x	x	..	x	x	13	13
Less than 9 mg	x	..	x	x	x	..	x	x	..	..	x	..	..	..	..	..	..	..	x	..	..	8	8
Decreased rate of gain:																							
Weight:																							
Before	..	..	..	..	..	..	x	x	..	x	x	..	..	..	..	..	..	..	..	..	..	4	4
During	x	x	x	x	x	x	..	..	x	..	..	x	x	x	x	..	x	x	x	x	x	16	16
After	..	..	..	x	..	..	..	..	..	..	..	..	..	..	x	x	..	x	..	..	..	4	1
Height:																							
Before	x	..	x	..	..	..	x	x	x	x	x	x	x	..	..	..	x	..	..	x	x	12	12
During	x	x	x	x	x	x	x	..	x	..	x	x	x	x	x	..	x	x	x	x	x	18	8
After	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	x	..	..	..	..	..	1	1
Capillary resistance test	—	—	±	—	—	—	—	—	—	—	—	0	0	0	0	0	0	0	0	0	0	1+ 11—	
Infections:																							
Moderate:																							
Before	..	..	x	..	..	x	x	x	..	x	x	x	..	x	..	..	..	..	..	x	..	9	9
During	x	x	..	..	..	x	x	..	x	x	x	..	..	x	x	..	..	..	x	x	x	12	6
After	..	..	..	..	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1
Slight:																							
Before	x	x	..	x	..	..	..	..	x	..	..	..	x	..	x	x	..	..	x	..	x	9	9
During	..	..	x	..	..	..	..	x	..	..	..	x	..	..	..	..	x	..	..	..	..	4	4
After	..	..	..	..	..	..	x	..	..	..	..	..	..	x	..	x	..	..	..	..	..	3	3
Eczema:																							
Before	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	x	x	..	..	..	2	2
During	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	x	..	..	..	..	1	0
Low hemoglobin content and red cell count:																							
Before	..	..	..	..	x	x	x	..	x	..	x	..	..	.	..	..	..	..	x	..	..	6	6
During	..	..	..	..	..	x	..	..	..	..	..	..	..	x	..	..	..	..	x	x	..	4	2
After	x	..	..	..	..	..	..	..	..	..	..	..	..	x	..	..	..	..	..	..	..	2	1

Appetite and nutrition:																							
Good	..	..	x	..	..	x	..	..	x	..	..	..	x	..	x	x	x	x	..	..	..	8	8
Fair	x	x	..	..	x	..	x	x	..	x	..	x	..	x	..	..	..	..	x	x	..	10	10
Poor	..	..	..	x	..	..	..	..	..	..	x	..	..	..	..	..	..	..	..	..	x	3	3
Vomiting:																							
Before	x	x	x	x	..	..	x	x	x	x	x	..	x	x	..	x	..	..	x	x	..	14	14
During	x	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	x	..	3	0
Diarrhea:																							
Before	..	..	..	..	x	..	x	x	..	..	x	x	x	..	..	..	..	..	..	..	..	6	6
During	..	..	..	..	..	..	x	..	..	..	..	x	..	..	..	..	x	..	..	..	..	3	1
Subcutaneous hemorrhage	x	x	..	..	x	..	..	..	..	..	x	..	..	..	..	..	..	..	..	x	..	5	5
Teeth erupted:																							
Before 6 months of age	..	..	..	..	..	2	..	..	..	1	1	..	..	2	..	2	4	..	..	..	..	12	6†
Before 8 months of age	..	..	2	2	..	4	2	..	..	4	4	2	..	4	..	6	7	1	..	..	..	38	5†
Before 12 months of age	4	4	6	4	0	7	7	4	1	11	8	4	0	6	5	9	12	5	2	2	2	103	8†
Prenatal history:																							
Good	..	..	..	..	..	..	..	x	x	x	..	..	..	x	x	x	x	x	x	x	x	11	11
Poor	x	x	x	x	x	x	x	..	..	..	x	x	x	..	..	..	..	..	..	..	..	10	10
Environment and management:																							
Good	..	..	..	..	..	x	x	..	..	..	..	x	..	..	..	x	x	..	..	..	x	6	6
Fair	x	x	x	..	..	..	..	x	..	..	..	..	x	..	..	..	..	x	x	..	..	7	7
Poor	..	..	..	x	x	..	..	..	x	x	x	..	..	x	x	..	..	..	..	x	..	8	8
Cooperation:																							
Good	..	..	..	..	..	x	x	x	..	..	x	x	..	..	x	x	x	x	x	x	x	12	12
Fair	x	x	x	..	x	..	..	..	x	x	..	..	x	..	..	..	..	..	..	..	..	7	7
Poor	..	..	..	x	..	..	..	..	..	..	..	..	..	x	..	..	..	..	..	..	..	2	2
Rickets on roentgen study:																							
Before	x	..	x	x	..	..	..	..	..	x	..	..	..	..	..	..	..	..	..	x	..	5	5
During	x	x	x	x	x	x	..	x	..	x	..	..	..	..	..	..	..	..	..	x	..	9	4
Craniotabes (or beading):																							
Before	x	x	x	x	x	x	..	..	x	x	x	x	x	x	x	x	..	x	x	x	..	17	17
During	x	x	x	x	x	..	..	..	..	..	..	x	x	..	..	..	..	..	x	x	..	9	0
Temperature	+	+	+	+	—	+	+	0	+	0	0	0	0	+	+	0	0	0	+	+	+	12+ 1—	

* Demonstrated according to Park's criteria. All tabulations are made with respect to the time during which mild scurvy was present.
† Indicates number of infants acquiring first teeth at this age.

The condition of 21 of the 427 normally controlled infants was diagnosed as mild scurvy. None of these children presented diagnostic clinical findings or any evidence of scurvy except the minute roentgen changes. The 1 infant (table 4, case 467) who had classic scurvy passed through a period of mild involvement in which the results of the examination were similar to those of the 21 babies with mild scurvy.

The infants recovered spontaneously, without any change in the diet or management. Detailed individual records were made the subject of an intensive protocol study by one of the staff (B. M. H.); the interrelated observations are tabulated in table 5.

From the table it will be seen that roentgen evidence of slight scurvy was present at or before the age of 6 months in 8 infants, at from 6 through 8 months in 11 infants and at from 8 through 12 months in 12 infants. There is overlapping of the figures because the findings were present on consecutive monthly observations in some cases. In no case were the roentgen signs of scurvy obvious except on careful scrutiny of the films.

Daily Vitamin C Intake.—The prepared formulas used in this study lost 17 to 33 per cent of their vitamin C content before feeding time (table 2). The ascorbic acid assigned to the 427 infants receiving the complete formulas approximated 10 mg. per day. From table 5 it may be noted that only 14 of the 21 infants in whom mild scurvy developed and healed spontaneously, as shown by periodic roentgen study, received an average of 9 mg. of ascorbic acid daily; 7 consumed less than this amount. As mild scurvy occurred in only 14 infants who were receiving an average of 9 mg. of ascorbic acid daily and in those cases healed spontaneously, it is reasonable to assume that the scurvy in these instances was due not to an inadequate supply of vitamin C but either to inefficient absorption of the ascorbic acid or to predisposition caused by some concurrent factor. The reasonable indication is that the minimal requirement of the average healthy infant lies near 10 mg. of vitamin C daily.

Height and Weight.—The accompanying chart shows that the composite curves for gain in height and weight for the 427 infants observed in this study conform satisfactorily with similar curves compiled by Stuart [38] from observations on a group of selected white infants and also with those for the cosmopolitan groups studied by the Children's Bureau.[39]

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38. Stuart, H. C.: Standards of Physical Development for Reference in Clinical Appraisement, J. Pediat. **5**:194, 1934.

39. Woodbury, R. M.: Average Heights and Weights of Children Under Six Years of Age, Publication 87, United States Department of Labor, Children's Bureau, 1921.

Comparing the average height and weight curves of the 21 babies with scurvy with curves for the composite group of 427 infants shows a slight difference in height in favor of the composite group and an average difference in weight of about 300 Gm. in favor of the composite group from about 3 through 12 months of age.

Examination of the individual records shows (table 5) that there was slowing in the rate of gain in weight in 4 of the 21 infants before scurvy was evident on roentgen study. In these cases infections of moderately severe degree were present. Sixteen of the 21, however, showed slowing or cessation of gain in weight at the time scurvy was evident on roentgen study. The normal gain in weight was resumed after the scurvy spontaneously healed, as evidenced by the fact that only 4 infants showed any appreciable retardation in increase of weight after disappearance of the roentgen signs. If so-called latent scurvy

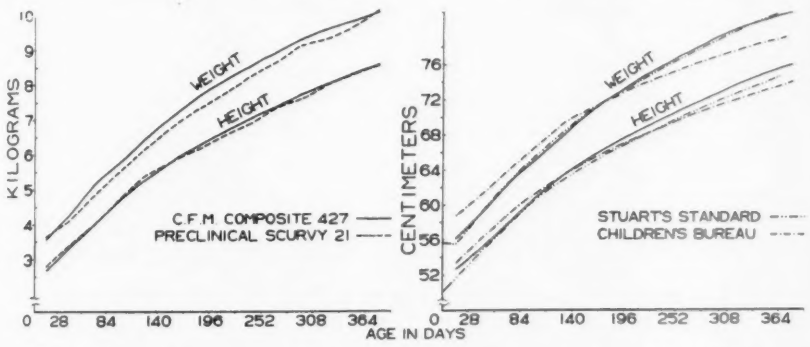

Chart.—Composite curves for gain in height and weight for 427 infants compared with those of 21 infants who showed preclinical scurvy and with similar curves compiled by Stuart and by the United States Children's Bureau.

was present before roentgen evidence appeared and after it spontaneously cleared, the disease did not affect the rate of gain in weight. The rate was affected only during the period in which definite mild scurvy was manifest. The average weight curve of the 21 infants is lower than that for the composite group because the definite mild scurvy in the individual infants is scattered through all age levels from 3 to 12 months.

Examination of the data for height in table 5 shows a more striking finding of similar nature. Twelve of the 21 infants showed slowing of the rate of growth in length before scurvy was evident on roentgen study. Only 7 of these had a moderately severe degree of infection which might have contributed to this slowing. All but 3 of the 7 and in addition 14 of the 21, a total of 18, showed slowing or cessation of gain in height at the time scurvy was manifest on roentgen study.

All infants resumed the normal rate of gain after disappearance of the roentgen signs of scurvy. From this it would appear that slight slowing in rate of gain in height is suggestive of developing scurvy. The fact that the normal rate of growth is resumed with disappearance of definite evidence of scurvy by roentgen diagnosis indicates that this effect is due to a definite scorbutic process rather than to a so-called latent condition caused by subnormal vitamin C intake.

These changes in rate of gain in weight and height were definite but slight; they were limited to specific short periods and were probably detectable only because accurate measurements were made at regular intervals and recorded in metric scale. These measurements were made by the same observers throughout the study, which produced the maximum accuracy in both the reading and the recording of the findings.

Capillary Resistance Tests.[27]—The results of the capillary resistance test (Göthlin's method), which was applied to 112 infants between the ages of 4½ and 8 months, are not so impressive as those reported by other investigators.[40] It is significant that 12 of these infants had roentgen evidence of scurvy, 7 of them at the time the test was made.

Age in Months	Number of Petechiae						
	0	1	2	3	5	7	Total
4½	1	..	..	..	..	..	1
5	39	4	6	1	..	1	51
5¼	2	..	..	..	..	..	2
5½	21	..	..	..	..	..	21
5¾	2	..	..	..	..	..	2
6	18	5	..	..	..	..	23
6½	2	..	..	..	..	..	2
7	3	1	2	..	1	..	7
8	..	..	2	1	..	..	3
Total	88	10	10	2	1	1	112

In case 467 (table 4), which was set aside from the group because the infant did not receive his allotment of vitamin C, no petechiae were seen at the age of 5 months. Three weeks later there was roentgen evidence of mild scurvy. At 7½ months the capillary resistance test showed 30 petechiae, and three weeks later roentgen examination showed extreme scurvy.

Entirely different results were obtained in case 16. The infant's roentgenograms showed evidence of a mild degree of scurvy at the ages of 5, 6½ and 12 months. A capillary resistance test was made at the fifth and at the sixth month. At 5 months the test showed 7 petechiae; at 6 months the test was negative. It seems that decrease in capillary

40. Göthlin.[14c] Dalldorf, G.: A Sensitive Test for Subclinical Scurvy in Man, Am. J. Dis. Child. **46**:794 (Oct.) 1933. Stocking R.: Application of the Capillary Resistance Test as a Measure of Vitamin C Nutrition, Arch. Pediat. **50**:823, 1933.

resistance occurs in cases of manifest scurvy at some stage of the process but that this is not true in cases of scurvy of mild degree or early involvement. Finer criteria of diagnosis indicate that the condition which was formerly considered latent scurvy is probably definite mild scurvy.

Infection, Vomiting and Diarrhea.—The subject of vitamin C and resistance to infection was summarized by Robertson [41] from the standpoint of animal experimentation and of clinical observation. Many of the experimental results concerning the effect of vitamin C on immunity and on the outcome of induced infection in states of efficiency are contradictory. Clinical interpretations are also contradictory, both as to susceptibility to infection and as to the reaction of persons deprived of the vitamin to disease processes. Great significance is given by writers to latent scurvy. However, they give no specific criteria for diagnosing manifest scurvy in interpreting the significance of infection in this state. It appears that the consensus is as expressed by Hess [3a]: Infection is the "most important condition which may suddenly and precipitously induce scurvy." Rational interpretation, however, seems to be confused by the fact that significance is given to conditions of so-called subnormal vitamin C intake and latent scurvy, without any specific mention of criteria for identification and classification of these states or for definition of the borderline between them and manifest scurvy.[3e]

From table 5 it will be seen that 18 of the infants with roentgen evidence of mild scurvy had moderate or slight infections either before or at the time that the condition was manifest. After spontaneous healing was evidenced by disappearance of roentgen signs, only 1 infant showed moderate infection; 3 others had slight infection. Of the 2 infants that had slight roentgen evidence of scurvy and did not have infection before or at the time that it was manifest, 1 had eczema and the other had a hemoglobin level below 10 mg. before scurvy was manifest.

It must be remembered that in these cases the mild scurvy cleared spontaneously during the same vitamin consumption with which it developed. The fact that the signs of scurvy disappeared coincidentally with the symptoms of infection during a constant intake of vitamin C would indicate definitely that the presence of infection predisposed the individual to the development of scurvy—either by diminishing the availability of the vitamin C consumed or by generally lowering the efficiency of the physiologic processes of the tissues. In these cases infection definitely cannot be interpreted as being a con-

41. Robertson, E. C.: The Vitamins and Resistance to Infection, Medicine **13**: 123, 1934.

comitant symptom of the scurvy process. A comparative analysis of tissues obtained at autopsy for the vitamin C content is presented in table 6.

Table 7 shows the occurrence of infection in the 21 babies with scurvy and as compared with that in the composite group of 427 infants. There were no deaths among the group with scurvy. One per cent of the 427 died of pneumonia.

Vomiting was sufficiently important to have been complained of and recorded for 14 of the infants who contracted scurvy. In all

TABLE 6.—*Analysis for Vitamin C Content of Tissues Obtained at Autopsy**

		Causes of Death			
	Normal†	Scurvy	Prematurity	Hemophilia	Diabetes-Nephritis
No. of cases	1	2	4	1	1
Age	20 months	10 months	..	3 years	10 years
	Milligrams per Gram of Tissue				
Tissue					
Adrenal	1.19	0.128	0.576	0.611	0.342
Brain	....	0.018 (1 only)	.....	0.183	0.077
Heart	0.09	0.006	0.016	0.025	0.007
Kidney	0.18	0.018	0.162	0.120	0.075
Liver	0.37	0.051	0.132	0.208	0.137
Lung	....	0.004	0.060	0.056	.....
Pancreas	0.30	0.015 (1 only)	0.142 (3 only)	.....	0.061
Spleen	0.34	0.018	0.170 (3 only)	0.315	0.127
Thymus	....	0.002	0.309 (3 only)	.....	0.014

* Autopsy was done eight to twenty hours after death.
† Bessey, O. A., and King, C. G.: The Distribution of Vitamin C in Plant and Animal Tissues, and Its Determination, J. Biol. Chem. **103**: 687, 1933.

TABLE 7.—*Occurrence of Infection*

	427 Babies—Composite Group—1933-1936			
	406 Babies Without Scurvy		21 Babies With Mild Scurvy	
	Total	Average per Baby	Total	Average per Baby
Nasopharyngitis:				
Mild	814	2.00	59	2.81
Moderate and severe	293	0.72	17	0.81
Otitis media	66	0.16	3	0.14
Bronchitis and pneumonia	75	0.18	..	....
Diarrhea	148	0.36	5	0.24
Specific diseases	105	0.26	6	0.29
Eczema	61	0.15	7	0.33

instances it was complained of before scurvy was evident on roentgen examination.

Diarrhea preceded the roentgen manifestation of scurvy in 6 of the 21 babies. Two of the 6 and 1 additional infant had diarrhea at the time the roentgen evidence of scurvy was observed. In all instances the diarrhea, and in most instances the vomiting, was a symptom of parenteral infection. In these cases the decrease in the amount of vitamin C available for absorption is undoubtedly an important factor in the development of mild scurvy.

Hemorrhage, Hemoglobin Content, Eczema and Fever.—Because the deficiency of intercellular cementing substance in advanced scurvy produces decreased capillary resistance, great significance has been placed on a tendency to bleed as an important symptom of lowered vitamin C intake and latent or manifest scurvy. The child who had advanced scurvy had subperiosteal hemorrhage. One of the 21 infants had infraorbital subcutaneous hemorrhage toward the end of the course of moderately severe pertussis during which the roentgen signs of scurvy were evident. A capillary resistance test was not done on this baby. One child had meningeal symptoms after a negative reaction to a capillary resistance test. Two months later the infant had fever and convulsions, and from findings in the spinal fluid a diagnosis of hemorrhagic encephalitis was made. Two months later roentgen evidence of scurvy was found. In 2 infants (twins) the teeth erupted slowly and the gums were swollen and painful over the incisors, without a hematoma, for two months before the teeth erupted. Capillary resistance tests gave negative reactions at the time scurvy was evident on roentgen examination. One infant had swollen hands at the time roentgenograms were taken which showed a slight osseous change suggesting scurvy. The mother attributed the swelling to frostbite due to lack of heat in her home, but possibly it was the transient edema of scurvy. The capillary resistance test gave a negative reaction. It is evident from these observations that a decrease in capillary resistance or a tendency to interstitial bleeding is not a reliable criterion for diagnosis of mild scurvy, as it is not a constant finding. The findings verify those of Hess,[3e] who stated: "In my experience there are decided individual variations in regard to the reaction to this test (capillary resistance) so that although it is true that petechial spots are far more numerous in individuals suffering from latent scurvy, the reaction cannot be used as an evidence of low vitamin C intake." It is possible that a combination of factors, including infection as well as subminimal utilization of vitamin C, are necessary for this effect on capillary resistance.

Anemia has been universally conceded to be associated with scurvy, but opinion differs as to the cause and the constancy of the symptom except with an advanced degree of scurvy. Seven of the 21 patients observed in this group showed a hemoglobin content of 10 Gm. or less per hundred cubic centimeters at the time or before signs of scurvy were detected by roentgen examination. One infant showed a drop in the hemoglobin level after clearing of the evidence of scurvy. All of these patients had had moderate or severe infections which possibly would have lowered the hemoglobin level, regardless of the utilization of vitamin C or the development of slight scurvy. The

patient with classic scurvy had normal values for hemoglobin. There is nothing in the analysis of the data on these 21 patients to indicate that a lowered hemoglobin level is any more a symptom of scurvy than it is a predisposing factor to its development.

The exudative diathesis of Czerny has been stated to be the only clinical condition which appears to predispose an infant to scurvy.[2] Two of the patients in this group had a mild degree of eczema before scurvy was detected on roentgen examination, 1 of them continuing to have it through infancy. Neither of these infants had had any infection of significance or any other factor which might have been considered as a predisposing cause for development of scurvy. It is probable that the condition responsible for the eczema was a factor in the predisposition of these 2 infants to have mild scurvy.

Twelve of the 13 infants who had temperature readings at the time the roentgen diagnosis was made showed elevation of temperature above normal. All but 1 of these had evidence of infection at the time.

Rickets, Teeth, Nutrition and Development.—Nine of the 21 infants had some roentgen evidence of rickets at the time a diagnosis of mild scurvy was made. It had been observed in previously taken roentgenograms in 5 cases. Craniotabes or beading was recorded as a clinical finding in 17 of the 21 cases at some time before mild scurvy was evident on roentgen examination. Nine of the infants had craniotabes or beading of the ribs at the time the roentgenogram showing scurvy was made. It would appear that there are predisposing factors common to both rickets and scurvy.

Growing teeth have been demonstrated to show histologic evidence of scurvy before it can be observed anywhere else in the body. We have found nothing in the literature which indicates that vitamin C has any effect on the time of eruption of teeth in infants. The data in tables 5 and 7 indicate that either scurvy or the conditions predisposing the infant to scurvy cause retardation of growth and of eruption of the teeth in infants. Three infants, examined at the ages of 2 and 3 years, showed deficiency of the crown enamel of the teeth which were erupting during the time that scurvy was manifest. McIntosh [3f] stated that, as far as can be determined, infantile scurvy does not predispose to subsequent dental caries or to pyorrhea in later childhood. Table 8 shows the comparison of the time of cutting the first teeth and the average number of teeth per infant per age interval between the composite group and the 21 babies with scurvy.

Nutrition and appetite were good in 8 of the 21 infants, fair in 10 and poor in only 3.

Development in sitting, standing, walking and talking was apparently unaffected, though roentgen examination showed slight evidence of

mild scurvy. No abnormal irritability was particularly noted by mother, nurse or examiner except with the case of advanced scurvy, which presented a classic picture.

Prenatal Environment, Management and Cooperation.—Prenatal factors possibly have some significance in predisposing an individual infant to scurvy, but they are difficult to evaluate. The mothers of 10 infants in this group of 21 were classed as having had poor prenatal

TABLE 8.—*Average Teeth per Baby per Age Interval and Age at Appearance of First Tooth*

Age Intervals, Days	1933-1936 Composite Group (427 Babies)			Group with Mild Scurvy (21 Babies)*		
	Number of Visits	Teeth		Number of Visits	Teeth	
		Total	Per Baby		Total	Per Baby
57-84	402	2	0.005			
85-112	393	7	0.018			
113-140	393	21	0.053	21	1	0.048
141-168	380	58	0.153	20	2	0.100
169-196	374	144	0.385	18	10	0.556
197-224	345	333	0.965	19	19	1.000
225-252	335	561	1.675	20	33	1.650
253-280	328	853	2.601	20	45	2.250
281-308	286	1,097	3.836	14	33	2.357
309-336	278	1,252	4.504	16	65	4.062
337-364	249	1,387	5.570	15	80	5.333
365-392	105	655	6.238	6	36	6.000
393-420	12	80	6.667			

	Composite Group	Group with Mild Scurvy
Age in days at appearance of first tooth:		
Range †	51-350	121-350
Mean	222.4	246.6‡
Standard deviation	51.9	60.4
Babies who had teeth when discharged	354	18
Babies discharged before first tooth erupted	73	3
Below age range (51-350 days)	3	0
Above age range (51-350 days)	7	0
Within age range—below mean	42	1
Within age range—above mean	21	2

* These 21 are included in the group of 427 who received lemon powder.
† Range is determined from the frequency distribution of ten day class intervals.
‡ Difference between mean ages is not statistically significant.

conditions and diet; 7 of them were in the 1933-1934 study, made at the time the depression was dominant. Five of these infants showed roentgen evidence of mild scurvy at or before the age of 6 months, 4 between 6 and 8 months and the other at 12 months. The early development of scurvy in these infants suggests the importance of prenatal factors such as vomiting, an inadequate diet, hemorrhage, heart disease and a rapid succession of pregnancies.

Reports of good, fair and poor environment and management are almost equally divided for this group of 21 infants with scurvy. Cooperation on the part of the mothers was considered by the nurse to be poor in only 2 of the 21 families, fair in 7 and good in 12.

SUMMARY

Four hundred and twenty-seven infants, comprising a cross section of the indigent and near-indigent class of Detroit, were studied during their first year of life. Eighty per cent of them were studied for nine months or longer. The children were in their home environment, and the investigation was closely controlled. Almost 10 mg. of vitamin C was made available to each infant daily by the addition of powdered lemon juice to the formula.

Analyses were made of the consistency of strength of the powder and the loss which occurred before feeding when the formula was made up in advance. The average vitamin C value of powdered lemon juice was found to be 0.84 mg. per gram, and the loss during the twenty-four hour period for which the formula was made up ranged from 17 to 33 per cent. The use of the powdered lemon juice as an antiscorbutic factor produced satisfactory results. It appears that the minimal protective dose of vitamin C for the average healthy infant is about 10 mg. per day.

Comprehensive examinations of each infant were made monthly or oftener. Like examinations were made by the same examiners throughout the study to eliminate personal variance. The examinations included complete histories, individual and maternal, meticulous measurement of the gain in weight and height and tabulation of all clinical findings pertinent to the growth and development of each infant. Over 4,000 examinations were made; 10,342 roentgenograms were examined for evidence of scurvy, rickets and mineralization, and blood counts and determinations of hemoglobin content were made throughout the study. Psychometric developmental examinations were made on 127 infants and capillary resistance tests on 112.

From the data on the 434 infants observed in this study, with utilization of the finer criteria for diagnosis, it appears that the condition which has usually been considered latent scurvy is actually definite mild scurvy. Such a distinction puts an entirely different interpretation on the evaluation and classification of symptoms and causes of scurvy. It seems that scurvy is a definite pathologic entity but does not become evident or retard development until the absence of the specific physiologic functions of the vitamin is manifest.

A condition of chronic mild scurvy may exist for several months, with spontaneous clearing and recurrence accompanied by its resultant retarding effects on cellular function and physiologic processes of tissues. The symptoms of severe manifest scurvy, comprising the classic entity of Barlow's disease, develop through a combination of factors, which include continued low utilization of vitamin C and diminished cellular metabolism in interrelated functions of the tissues as a result

of infection, allergy or glandular heritage. There is a distinct variability in individual susceptibility; this is determined by prenatal as well as postnatal factors.

It is believed that during the course of the study 21 infants had mild scurvy, according to the criteria of Park and others. During the time mild scurvy was present the rates of gain in weight and height were retarded, but development in sitting, standing, creeping, walking and talking was not. From the results it appears that an infection predisposes to mild scurvy but is not a concomitant symptom of the condition. The amount of vitamin C absorbed may have been influenced by diarrhea and vomiting, when they were present as symptoms of parenteral infections. Lowering of the hemoglobin level does not appear to be a symptom of mild scurvy, nor does it predispose to the development of this disease.

A supplemental study is presented of 7 infants who received only the amounts of vitamin C contained in evaporated milk (approximately 2.5 mg. daily) for the first few months of life. No conclusions may be drawn from so few subjects; however, the findings agree with those obtained for the larger group.

COMPARATIVE STUDY OF THE TUBERCULIN PATCH TEST AND THE MANTOUX INTRACUTANEOUS TEST

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AND
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In our first communication [1] we demonstrated that from the point of view of reliability our tuberculin patch test is at least equal, if not superior, to the Pirquet test. Routinely the testing of larger groups is done not with the Pirquet but with the Mantoux test. The solution used is a 1:1,000 dilution, of which 0.1 cc. is injected. As the amount of tuberculin is greater than the amount absorbed when the Pirquet test is applied, the larger number of positive reactors can readily be understood.

Dr. Béla Schick has frequently pointed out that the one disadvantage of using the Mantoux test (0.1 mg.) routinely lies in the fact that often intensive local reactions and a rise in body temperature are observed—symptoms which should certainly be avoided. It was therefore thought desirable to have a test which would approximate the reliability of the Mantoux test (0.1 mg.) and at the same time eliminate unpleasant reactions. For this purpose we decided to increase the potency of the tuberculin patch test. This seemed justified, as in our one year's experience with the tuberculin patch test we have never seen an untoward reaction.

The tuberculin patch test as previously described has been modified (1) by the use of tuberculin produced from a synthetic medium [2] (Bureau of Animal Industry), which is about four times stronger than the old tuberculin prepared by the New York Department of Health which was formerly used, and (2) by the use of two squares of filter paper saturated with tuberculin on each piece of adhesive tape instead of the single square used in many of the former experiments with the test.

From the pediatric service of the Mount Sinai Hospital and the Sea View Hospital (chief of staff, Dr. Béla Schick).

1. Vollmer, H., and Goldberger, E. W.: New Tuberculin Patch Test, Am. J. Dis. Child. **54**:1019 (Nov.) 1937.

2. Siebert's medium. See Siebert, F. B.: The Isolation and Properties of the Purified Protein Derivative of Tuberculin, Am. Rev. Tuberc. **30**:713, 1934.

These modifications made it feasible to compare the tuberculin patch test with the Mantoux test as performed with purified protein derivative as well as with old tuberculin.

Without any exception, we tested all of the 169 tuberculous children of the Sea View Hospital, Staten Island, N. Y. First the tuberculin patch test and the Mantoux test with the first strength solution of purified protein derivative were made simultaneously. Subsequently the negative reactors to both of these tests were retested, after three days, with the second strength solution of purified protein derivative and with a second tuberculin patch test. The results were as follows:

Number of Cases	Purified Protein Derivative I	Patch Test	Purified Protein Derivative II	Second Patch Test
164	+	+	Not done because not necessary	
1	—	+	Not done because not necessary	
2	—	—	—	—
1	—	—	+	—
1	—	—	+	+
169				

This tabulation does not require further explanation. Of 169 children with active tuberculosis, only 1 failed to react positively to the tuberculin patch test who reacted positively to the Mantoux test with the stronger solution of purified protein derivative.

Furthermore, in the pediatric service of the Mount Sinai Hospital we applied the tuberculin patch test routinely to every child admitted to the wards over a period of four and one-half months. First the Pirquet test and the patch test were done simultaneously. The negative reactors were retested by the Mantoux test with 1 mg. of old tuberculin prepared by the New York Department of Health. The results are shown in the following tabulation:

Number of Cases	Pirquet Test	Patch Test	Mantoux Test, 1 Mg.
106	—	—	—
8	+	+	Not done
2	?	+	Not done
2	—	+	+
118			

This series is too small to justify unreserved conclusions. However, it shows that among this group of 118 children the Mantoux test, even with 1 mg. of old tuberculin, did not reveal a single case of tuberculous infection which was not already discovered by the tuberculin patch test.

For the purpose of studying this question, this stronger tuberculin patch test will be compared routinely with the simultaneously applied Mantoux test (0.1 mg.) in the pediatric service of the Mount Sinai Hospital and the Sea View Hospital. Only negative reactors to both of these tests will be retested by the Mantoux test with 1 mg. (0.1 cc. of the 1 : 100 solution being used). This procedure will make it possible to answer the important question whether or not the Mantoux test with 0.1 mg. of old tuberculin can be entirely replaced by the tuberculin patch test.

In none of the tests reported here, although some were done on patients with extremely acute tuberculosis, was any general constitutional reaction to the tuberculin patch test observed.

SUMMARY

1. Of 169 children with active tuberculosis, only 1 failed to react positively with the tuberculin patch test who reacted positively to the Mantoux test with the stronger solution of the purified protein derivative.

2. Among 118 children admitted to the wards with various diseases, the Mantoux test, even when 1 mg. of old tuberculin was used, did not reveal a single case of tuberculous infection which had not already been discovered by the tuberculin patch test.

25 Central Park West, New York.

Sea View Hospital, Staten Island, N. Y.

Case Reports

AURICULAR FIBRILLATION IN INFANCY

REPORT OF ITS OCCURRENCE IN A THREE MONTH OLD INFANT, PERHAPS STARTING BEFORE BIRTH

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AND
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Many clinical conditions that were considered unusual a generation ago are now known to be relatively common. Thus auricular paroxysmal tachycardia, auricular flutter and auricular fibrillation are being recognized so frequently in adults that observers report the cases in groups of a hundred or more. However, it is doubtful whether the discovery of any of these forms of arrhythmia in an infant will ever be other than rare. A thorough search of the literature has not revealed a report of a case of auricular fibrillation in an infant in the first year of life; the case presented here is therefore the first of its kind to be reported.

REPORT OF CASE

A girl was delivered by cesarean section in the eighth month of gestation because the mother had fibromas. The pregnancy was normal in all other respects, and there was no suggestion of toxemia. At birth the infant had a very rapid heart rate, but no note was made of the rhythm. Subsequently both the mother and the attending physician, Dr. S. W. Howard of St. Albans, Vt., observed marked irregularity as well as tachycardia. The mother also noticed that when the heart rate was extremely rapid the baby grunted with each breath; these periods lasted only a few seconds or minutes, but recurred frequently. The infant's hands and feet were usually cold and slightly bluish. Her appetite and general progress were not alarmingly bad, but they were not entirely satisfactory. Tolerance for food was capricious; gain in weight was slow. When about 2 months old the baby exhibited general cyanosis of moderate degree for several minutes, causing the parents much anxiety.

We first saw the infant on June 25, 1935, when she was 3 months old. Her general appearance was normal. The face was rather pale. There were no signs of congestive cardiac failure. The spleen was not palpable. The reflexes were normal. There was no suggestion of cyanosis of the lips or extremities. Relative cardiac dulness was within normal limits. Auscultation revealed a rapid, absolutely irregular rhythm, suggestive of auricular fibrillation. The variations in loudness and duration of the heart sounds and the absence of murmurs can be described by the graphic method (fig. 1) more clearly than by words. The rate could not be counted satisfactorily during the frequent brief episodes of great rapidity. About 200 beats were counted in 1 minute by auscultation over the precordium and about 120 by palpation of the brachial artery.

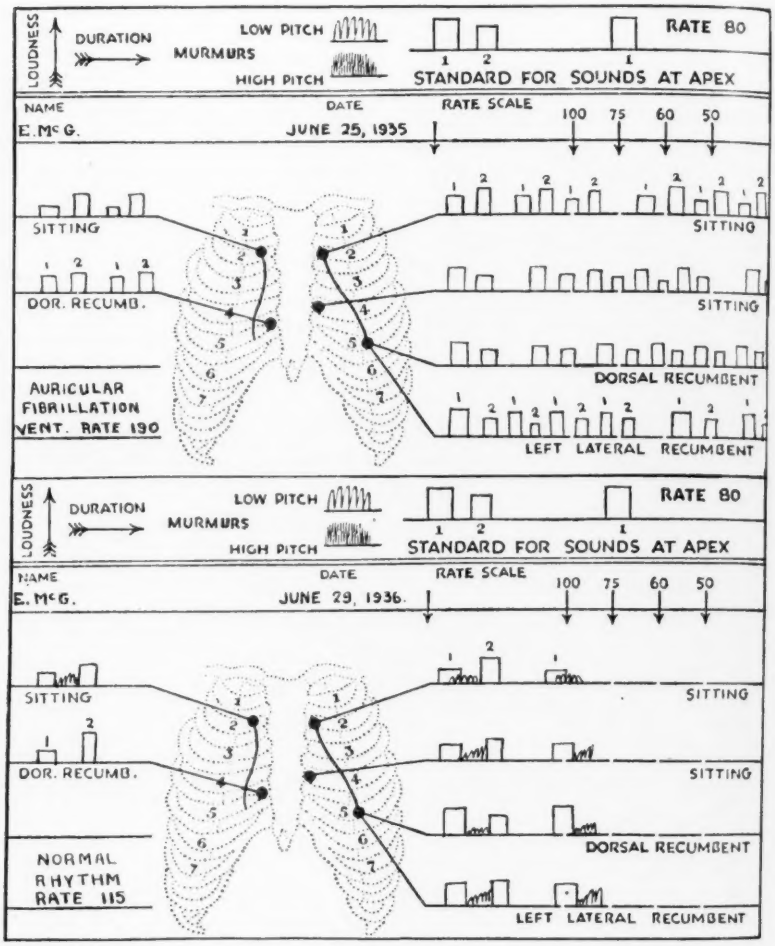

Fig. 1.—Graphic representation of the heart sounds. Note the short, sharp first and second sounds during auricular fibrillation. The loudness and duration of each sound are less during extremely rapid fibrillation and somewhat greater after longer periods of diastole. No murmur was heard during auricular fibrillation. The heart sounds during normal rhythm are somewhat longer and louder than during auricular fibrillation, but the relative loudness of the first and second sounds at the various sites of auscultation is the same during arrhythmia and during the normal rhythm. A short, late, rough systolic murmur was heard between the first and the second sound, but no diastolic murmur was noted during normal rhythm. These records were made on sticker charts for graphic description of heart sounds and murmurs (printed by Sanborn Company, Cambridge, Mass., and by S. Share, Montreal). A description of this method of recording has been published (Segall, H. N.: Auscultation of the Heart, Canad. M. A. J. **27**:632, 1932; A Simple Method for Graphic Description of Cardiac Auscultatory Signs, Am. Heart J. **8**:533, 1933).

The electrocardiogram (fig. 2*A*) demonstrated auricular fibrillation. The auricular rate was between 500 and 750 per minute; the maximum interval between two auricular waves was 0.12 second, the minimum interval 0.08 second and the average variation of these intervals 0.008 second. Intervals in which the auricular waves were of good amplitude alternated irregularly with intervals in which the base line was finely irregular and auricular waves were not sharply defined. The maximum ventricular rate was 300 and the minimum 100 per minute; the average rate, computed by counting beats recorded continuously for

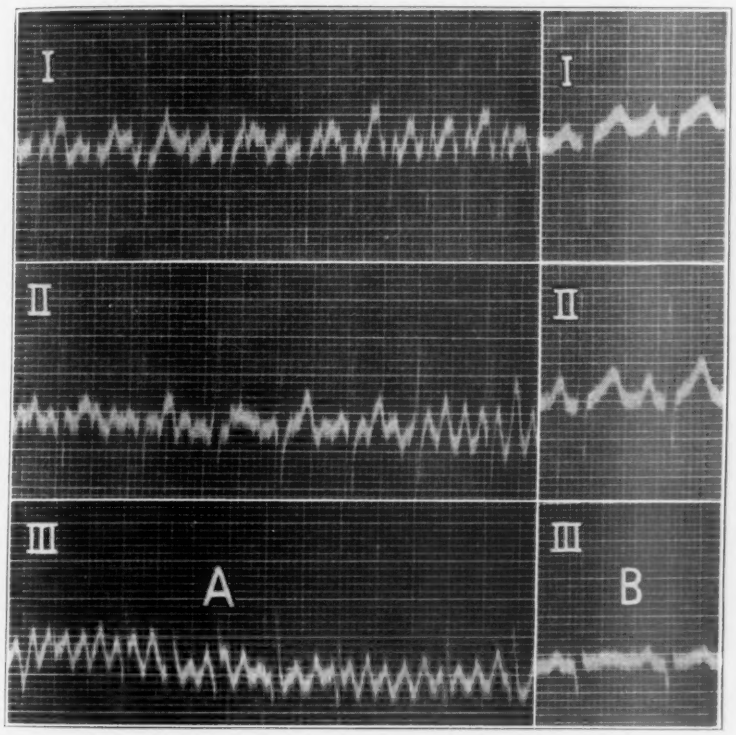

Fig. 2.—*A*, electrocardiogram taken June 25, 1935, showing auricular fibrillation, an average ventricular rate of 190 and an upright T wave in all leads. Note that in lead III the fourth ventricular complex, reading from the left, is of unusually high voltage. This may represent a ventricular ectopic beat. *B* was taken on June 29, 1936. The rhythm is normal, the rate 115, the PR interval 0.16 second and the QRS interval 0.06 second. The T wave and electric axis are normal. Note that the QRS complexes in leads I and II are similar during arrhythmia and normal rhythm but that in lead III the QRS voltage is lower during arrhythmia than during normal rhythm. This may, however, be due to some material changes that occurred in the size and shape of the heart in the course of a year.

90 seconds, was 190 per minute. The configuration of six ventricular beats suggested that they were ectopic.

An adequate trial of pressure on each eyeball and over each carotid sinus failed to restore normal rhythm and caused no apparent change in ventricular

rate. The baby was digitalized and then received maintenance doses of digitalis. Five minims (0.3 cc.) of digitol given four times daily for a week brought about slowing of the ventricular rate to 120 per minute (counted by auscultation over the precordium). During this week the general condition improved remarkably. Respiration became normal, the hands and feet were warm and no trace of cyanosis could be discerned. The appetite improved greatly, and tolerance for food was normal. Five minims of digitol given three times daily maintained the heart rate at about 120. This amount is equivalent to 1 frog unit per day, which is only a fraction less than the average maintenance dose for an adult.

When the child was 5 months old she was brought to us again. The electrocardiogram at this time showed no change in auricular rhythm or rate; the ventricular rhythm was absolutely irregular, as before, but the rate was 150 per minute. It is likely that the rate was usually slower than we found it, after the baby's 75 mile trip to Montreal. The T wave in leads I and II of this record is of much lower voltage than that in the first record; this is objective evidence of the effect of digitalis on the ventricular myocardium.

It was then decided to try quinidine sulfate. The use of digitalis was discontinued for a week; then ½ grain (0.03 Gm.) of quinidine sulfate was given every hour for five hours. This brought about vomiting; the child appeared so sick that Dr. Howard discontinued the treatment, and she was digitalized again. When the child was 1 year old, normal rhythm became established and digitalis therapy was stopped.

At the age of 15 months she swallowed a safety pin, which was removed surgically (gastrotomy) with the aid of local anesthesia. The cardiac rhythm remained normal during this episode, and the child proved to be a good surgical risk. Her parents brought her to us when she was 18 months old, and we found her to be a healthy, thriving baby. There had been no episodes of general cyanosis, but occasional grunting with respiration did occur. In addition, the parents observed the following peculiar syndromes: About once a fortnight the left leg and heel would suddenly become blue; this color would persist for only a few minutes. Nearly every day the child had periods of rigidity lasting a few moments, during which the hands were clenched and she grunted with each breath. The episodes ended when someone attracted her attention aggressively by making a noise or by shaking her. Physical examination revealed good nutrition, normal breathing and no cyanosis. Relative cardiac dulness was normal; the heart sounds were duller and longer than previously. A short, late systolic murmur about one-third the loudness of the first sound at the apex was detected; it could be heard all over the precordium but was loudest at the apex; no third sound or diastolic murmur could be discovered (fig. 2*B*). The rhythm was normal. An electrocardiogram revealed sinus rhythm with a rate of 115; the PR interval was 0.16 second and the QRS interval 0.06 second; the T wave and the electric axis were normal.

In September 1937 Dr. Howard reported that the child had not had any illness, that the cardiac rhythm remained normal and that in all respects she was normal for her age of 2½ years.

ETIOLOGY

This case offers no clue to a well defined etiologic factor. It is most likely that auricular fibrillation began at birth or at some time during fetal life. As the infant was delivered by cesarean section in the eighth month, she did not suffer from the usual strains associated with normal parturition. This lends weight to the suspicion that auricu-

lar fibrillation began during fetal life. At no time did the child present evidence of congenital cardiac malformation or of any constitutional disease. Thus the arrhythmia must have been caused by some unusual disturbance of the mechanism of the cardiac pacemaker. It is worthy of note that, with rare exceptions,[1] in the numerous reported cases of congenital heart disease, with or without cyanosis, auricular arrhythmia such as paroxysmal tachycardia, flutter or fibrillation was not exhibited. Of the infants with normally formed hearts who showed these arrhythmias, none was syphilitic. Furthermore, although the myocardium of syphilitic fetuses is known to contain abundant spirochetes, reports on syphilitic infants do not mention serious auricular arrhythmia as a feature of the clinical picture. The great rarity of these forms of arrhythmia in the newborn, together with the absence of any objective evidence of disease in most of the cases reported, indicates that the etiologic factor is concerned with a congenital abnormality of the pacemaker mechanism which cannot be clearly defined at present.

CONSTITUTIONAL EFFECTS OF AURICULAR FIBRILLATION

Clearly, the general effects of arrhythmia in this case are directly related to ventricular tachycardia and not to the rhythm or rate of the auricles. From birth until she was digitalized at the age of 3 months, the baby was sickly. She did not take feedings well; there were frequent episodes of peculiar grunting, labored respiration; the feet and hands were cool and slightly bluish, and on one occasion there was an alarming degree of general cyanosis for several moments. After the average ventricular rate was reduced from about 200 to 120 per minute by digitalization, all these symptoms disappeared and the infant thrived. No significant change was noted in the general condition after the twelfth month, when normal rhythm was established. The occasional episodes of grunting respiration and the periods of rigidity occurred during the nine months of digitalis therapy and did not disappear with the development of sinus rhythm.

During the first three months of life, those objective clinical signs which are commonly found in adults suffering from congestive cardiac failure were entirely absent. There were no rales over the lungs, no evidence of enlargement of the liver, no signs of edema of the skin and no engorgement of the jugular veins. These features might have appeared if the ventricular tachycardia had continued for a longer time.

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1. Schuster, N. H., and Paterson, D.: Specimen from Paroxysmal Tachycardia in Infant, Aged Nine Weeks, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **17**:11, 1924. Amberg, S., and Willius, F. A.: Auricular-Flutter with Congenital Heart Disease, Am. J. Dis. Child. **32**:99 (July) 1926.

THERAPY

Pressure on the eyeballs and over the carotid sinuses caused no change in the rhythm or rate of either the auricles or the ventricles. In adults also these procedures usually fail to restore normal rhythm in cases of fibrillation, but they are frequently effective in cases of auricular paroxysmal tachycardia and of auricular flutter. On one day half a grain of quinidine sulfate was given every hour for five hours; this caused vomiting and general illness but did not change the rhythm. Apparently the child could not tolerate quinidine sulfate. This drug might perhaps have initiated normal rhythm if she could have taken it comfortably for several days. Digitalization reduced the ventricular rate from about 200 to 120, but the rhythm remained irregular; the auricular waves were the same as before digitalization for at least two months (no electrocardiograms were recorded during the last seven months of digitalis therapy). Normal sinus rhythm became established for no apparent reason, as so often happens in cases of paroxysmal auricular or ventricular arrhythmia in older children and adults. Digitalization caused flattening of the T wave in leads I and II of the electrocardiogram, an effect well known in tracings of adults.

PROGNOSIS

Even when prognosis is discussed on a basis of many years' experience with a large number of cases, many verbs must be couched carefully in the subjunctive mood. It would therefore appear rather audacious to do more than acknowledge our ignorance concerning the probable outcome in a case of auricular fibrillation of congenital origin observed in infancy. However, our experience in this case indicates that this type of arrhythmia is not fatal and that it may give way to normal rhythm spontaneously. Moreover, digitalization is an effective therapeutic measure for the relief of the illness which results from ventricular tachycardia. One of us (H.N.S.) has observed an adult, who is now 52 years old, for the past eight years. Since early childhood this man has had arrhythmia which was recognized as perpetual arrhythmia when he was 16 and was shown to be auricular fibrillation when he was 35. He has not taken digitalis regularly because he has found that it makes no difference when he is in his usual healthy state. The average ventricular rate without digitalization is 100 per minute. It may be that he has had the arrhythmia since birth and that in the course of years the ventricular rate has spontaneously diminished because of fatigue of the bundle of His. This patient is mentioned because auricular fibrillation without evidence of heart disease is not rare in adults, and the patient in the case presented here may have a similar fate if auricular fibrillation should recur and persist. Judging

from our large experience with adults, we think it likely that this child will have paroxysms of auricular arrhythmia at various times in the course of her life and that auricular fibrillation or pure flutter will eventually become permanent. Lewis [2] recently reported the case of a man of 78 years who had auricular flutter persistently since the age of 50 and who has had paroxysms of tachycardia since boyhood. In 1935 there appeared a letter [3] from a person aged 82 years who had had attacks of paroxysmal tachycardia dozens of times a year and constant extrasystoles in the intervals between these episodes since the age of 10.

While the histories of these cases portend long life and adaptation to whatever disability the arrhythmia may cause in such patients, there are more sinister possibilities as well. The relative inactivity of the auricles favors formation of thrombus, and emboli from either the right or the left auricle may cause serious acute illness followed by disablement or even death. The danger of embolus becomes most significant when, after flutter or fibrillation has persisted for many years, normal rhythm is reestablished. Any other treatment than digitalization would therefore be inadvisable in such cases.

SUMMARY

Auricular fibrillation was demonstrated in an infant aged 3 months. The history strongly suggests that this arrhythmia existed at birth. Digitalization effectively reduced the ventricular rate and thus relieved the relatively mild symptoms. Normal rhythm was restored spontaneously in the twelfth month and has persisted; the child was last examined at the age of 2½ years.

Dr. S. W. Howard gave us permission to observe and report this case.

2. Lewis, T.: Auricular Flutter Continuing for Twenty-Four Years, Brit. M. J. **1**:1248 (June 19) 1937.

3. Extrasystoles, correspondence, Brit. M. J. **2**:357 (Aug. 24) 1935.

EMBRYONAL CYST OF THE WALL OF THE STOMACH

REPORT OF A CASE IN WHICH SYMPTOMS OF PYLORIC OBSTRUCTION OCCURRED

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In the case to be presented, a cyst as large as a hen's egg was situated on the greater curvature of the stomach near the pylorus, causing symptoms of pyloric obstruction. The rarity of this anomaly justifies this report.

A review of the literature reveals only 1 report of a case of congenital cyst of the stomach; this was presented by Lyon.[1] He stated that an infant 3 weeks of age with a history of vomiting from birth had a large, freely movable mass in the upper part of the abdomen. Operation revealed a cyst, measuring 3½ by 2½ inches (8.9 by 6.3 cm.), on the greater curvature of the stomach, extending over the pylorus. The report is brief, and no detailed data are given of the histologic characteristics of the wall of the cyst. Chemical examination of the contents of the cyst was not reported, although aspiration was performed several times before operation.

REPORT OF THE CASE

E. F. was born on May 6, 1931. She was the fifth child of healthy parents; all the previously born offspring were alive and well. Pregnancy and delivery were normal; the weight at birth was 6 pounds and 4 ounces (2,835 Gm.). There were no neonatal complications. Physical examination after birth gave entirely negative findings. The patient was referred to me on July 7, 1933, at the age of 26 months, with a history of vomiting for twelve days. Her appetite was poor, the bowels were constipated and urination was infrequent and scant. She was restless, slept poorly and had lost 5 pounds (2.3 Kg.) since the onset of her illness. There had been no rise in temperature at any time. She was pale (hemoglobin content, 60 per cent). The urine was entirely normal. The abdomen was distended but soft, and the edge of the liver was palpable at the level of the umbilicus. In the right upper quadrant to the right of the midline was palpated a tender cystic mass; it had the size and shape of a large egg and was slightly movable. There was no evidence of spasm, tenderness or tumor in the region of the appendix.

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1. Lyon, W.: A Case of Congenital Cyst of the Stomach, Tr. Clin. Soc. Univ. Michigan, 1916, p. 7; J. Michigan M. Soc. **15**:42 (Jan.) 1916.

On July 11 the tumor was still palpable, but the liver had receded somewhat. Vomiting was less marked. The infant was hospitalized for further study at the Brooklyn Jewish Hospital, where the following data were obtained:

A roentgenogram (flat plate) of the abdomen showed an indistinct mass in the region of the right kidney. An intravenous pyelogram showed no delay in excretion of dye on either side. The pelves, calices and ureters were normal. No calculi were present. The right kidney seemed slightly larger than the average.

Gastrointestinal study showed that the stomach emptied in two hours. There was no evidence of obstruction. The outline of the stomach was normal; there was no evidence of a diverticulum. Intestinal motility was normal. There was no evidence of obstruction in the large bowel, as practically all the barium sulfate was evacuated in twenty-four hours. The pulmonary fields and pleural markings were normal on roentgen examination. The diaphragmatic cusps were not elevated.

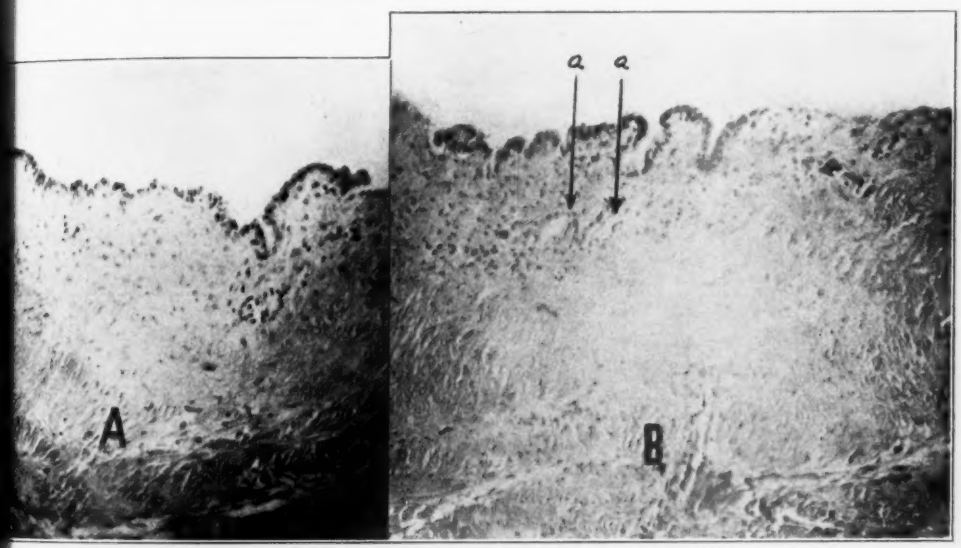

Fig. 1.—*A*, low power view of the wall of the cyst, showing lining epithelium and underlying loose fibrous stroma, which contains occasional blood vessels surrounded by small round cells. This stroma rests on a thick fibrous wall. *B*, low power view, showing glandlike spaces deep in the stroma (*a* indicates cystic dilatation of branching pancreatic ducts?).

Wassermann and Kahn tests of the blood gave negative reactions. The hemoglobin content was 62 per cent, the red blood cell count was 4,210,000 per cubic millimeter and the white blood cell count was 10,750; there were 61 per cent polymorphonuclears and 39 per cent lymphocytes.

Cultures of material from the throat and nose were negative for Bacillus diphtheriae. A vaginal smear was negative for gonococci. The Schick test gave a positive and the Dick test a negative reaction. Tuberculin tests gave negative reactions with dilutions of 0.1, 1 and 5 mg. per cubic centimeter.

Examination of urine and stools revealed no abnormality.

On surgical consultation the diagnosis was congenital cyst, possibly of the right kidney or of the mesentery; operation was advised. As vomiting, nausea and pain had suddenly stopped, the parents decided to wait before submitting the child to an operation.

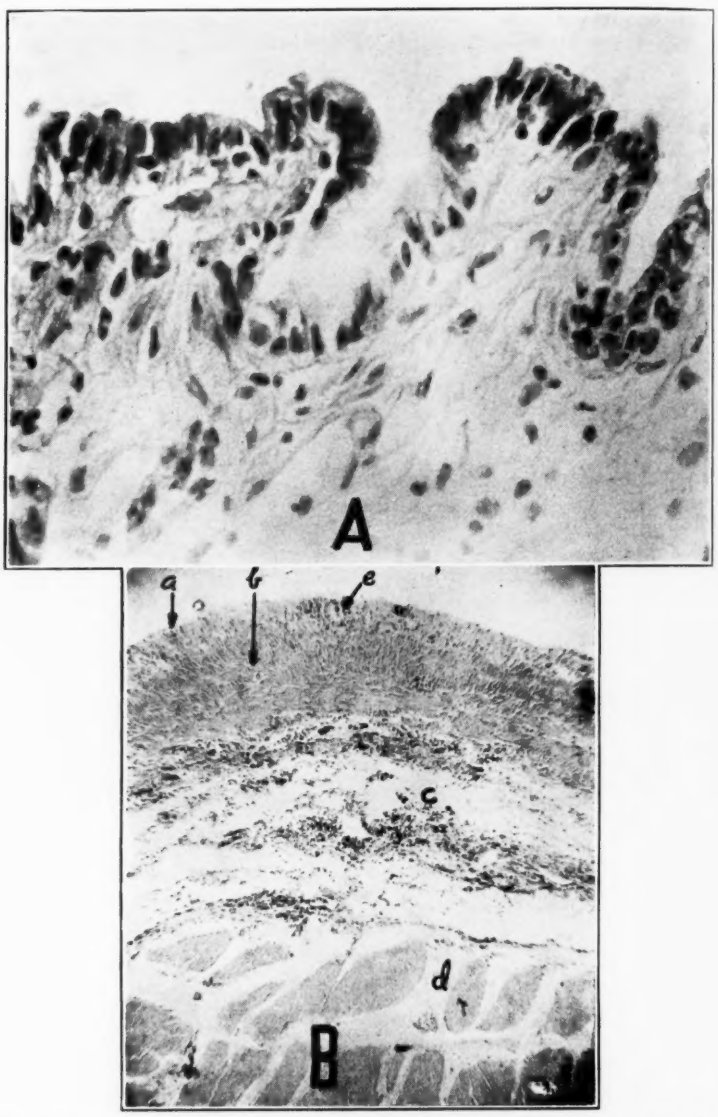

Fig. 2.—*A*, high power view of lining epithelium and stroma, showing tall columnar epithelium and occasional mucus-containing cells. *B*, topographic view, showing the wall of the cyst. *a* indicates epithelium denuded in this view; *b*, fibrous tissue stroma; *c*, loose connective tissue, showing dense infiltration with small round cells; *d*, muscle bundle layer; *e*, dilated duct.

For the next six months the patient seemed fairly well, ate better and had only an occasional attack of vomiting and discomfort. In February 1934 a sudden acute attack occurred, with vomiting, epigastric pain and constipation, and on February 20 the child was operated on by Dr. John F. Erdmann at the New York Post-Graduate Medical School and Hospital. He reported:

"On operation I discovered one of the rarities in the surgical field in children—a cyst the size of a hen's egg on the greater curvature of the stomach, which was making compression on the pylorus similar to pyloric stenosis. I was able to deliver this cyst with some trouble, but at the same time all was completely removed."

The pathologic diagnosis, concurred in by several pathologists, was embryonal cyst, apparently of pancreatic duct origin, showing subacute inflammation.

The child made an uneventful recovery after the operation. Three years and eight months later the patient was in excellent health. No recurrence of nausea, vomiting, epigastric pain or tumor mass had been noted.

Since Klob [2] and Zenker,[3] over seventy-five years ago, reported the first cases of aberrant pancreatic tissue in man, more than a hundred additional reports have appeared in the literature. In all cases the growth was accidentally found during the course of an abdominal operation or at autopsy. With few exceptions it occurred in adults. The youngest patient with an aberrant pancreas was one reported on by Hale [4] in 1926; the cyst was situated in the pyloric wall of a 6 week old infant, causing pyloric obstruction. Gardiner,[5] in 1907, found an aberrant pancreas in the wall of the stomach of a 3 month old infant; it produced a congenital hourglass deformity. Hess,[6] in 1912, reported this anomaly in a 3 month old infant who died of congenital obliteration of the bile ducts. Five reports of children from 12 to 15 years of age have been mentioned. Practically all the other cases reported have been those of adults from 21 to 72 years of age.

In all reports the accessory pancreas is described as a nodule or tumor in the muscular coat of the stomach or intestine; it is usually small, the average diameter being about 4 cm.

In 111 cases reviewed, 41, or 37 per cent, of the cysts occurred on the wall of the stomach and 46, or 41.4 per cent, on that of the duodenum and of the first 8 inches (20 cm.) of the jejunum. Its distribution on the

2. Klob, J.: Pancreas-Anomalien, Ztschr. d. k.-k. Gesellsch. d. Aerzte zu Wien **15**:732, 1859.

3. Zenker, F. A.: Nebenpancreas in der Darmwand, Virchows Arch. f. path. Anat. **21**:369, 1861.

4. Hale, K.: A Study of the Accessory Pancreas, Ann. Surg. **83**:774 (June) 1926.

5. Gardiner, J. P.: A Case of Congenital Hour-Glass Stomach with Accessory Pancreas, J. A. M. A. **49**:1598 (Nov. 9) 1907.

6. Hess, A. F.: A Consideration of the Pancreas and Its Ducts in Congenital Obliteration of the Bile Ducts, Arch. Int. Med. **10**:37 (July) 1912.

wall of the stomach, according to Delhougne,[7] is: pylorus, 58.3 per cent; greater curvature, 12.5 per cent; lesser curvature, 20.8 per cent, and cardia, 8.3 per cent.

Accessory pancreatic tissue usually occurs as a tumor with ducts, collections of acinar cells and frequently islands of Langerhans; i. e., it is typical pancreatic tissue. In many cases the stroma of the lobules is in excess of that found in the normal organ, giving a picture of chronic interstitial inflammation. Evidence of inflammation is also shown by collections of small round cells in the stroma or in the ducts. Atrophy of the parenchyma may be present. In cases in which the pancreatic parenchyma has undergone extensive atrophy, the ducts alone may be preserved.

Cordua [8] stated that "accessory pancreatic tissue may undergo cystic change and give rise to cysts. Such cases are not reported in the literature but the possibility of such an occurrence must be borne in mind."

Cystic dilatation of some of the collecting ducts, of microscopic degree, was mentioned by Thorel.[9]

Delhougne [7] reported 1 case in which the ducts enlarged and caused a cystic formation resembling adenomyoma.

Warthin [10] stated that "small nodules consisting of unstriped muscle and connective tissue are often found in the stomach wall. Occasionally one containing anomalous ducts, lined by columnar cells is found; or the nodule presents the picture of an adenoma. As transition stages exist between such myomatous or adenomyomatous nodules and those containing pancreatic tissue, the assumption is justified that the former represents accessory pancreatic tissue in which the parenchymatous portions are not developed, or have undergone retrograde changes leaving in one case the ducts, in the other the stroma and muscle alone." This assumption was also stated by Thorel,[9] Opie [11] and others.

Woolsey and Millzner [12] described types of adenomyoma of the stomach with pancreatic acinar cells and ducts. They stated that "in some cases the connection of the epithelial bud with the lumen of the stomach becomes lost, and either single or multiple cystic cavities result. These can be considered adenomyomas only if the cystic spaces are

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7. Delhougne, F.: Ueber Pancreaskeime im Magen, Arch. f. klin. Chir. **129**:116, 1924.

8. Cordua, cited by Thorel.[9]

9. Thorel, C.: Histologisches über Nebenpankreas, Virchows Arch. f. path. Anat. **173**:281, 1903.

10. Warthin, A. S.: Two Cases of Accessory Pancreas (Omentum and Stomach), Physician & Surg. **26**:337, 1904.

11. Opie, E. L.: Disease of the Pancreas: Its Causes and Nature, Philadelphia, J. B. Lippincott Company, 1903, ed. 2, 1910.

12. Woolsey, J. H., and Millzner, R. J.: Adenomyoma of Stomach, Arch. Surg. **16**:583 (Feb.) 1928.

lined by epithelial cells similar to those of the undifferentiated type of alveoli and show proliferative tendency."

In the case reported here the cyst was probably due to obstruction of the main duct of an accessory pancreas, with subsequent compression and atrophy of the pancreatic parenchyma. The columnar epithelium lining the cavity of the cyst, the presence of smaller ducts in the interstitial connective tissue, the muscle bundles which formed a more or less definite layer outside the fibrous and connective tissue and the evidence of inflammation (blood vessels surrounded by lymphocytes, mononuclear cells and polymorphonuclear leukocytes, and abundant stroma) all lead to a diagnosis of cyst formation in an accessory pancreas. Microscopic evidence of pancreatic acini and islands of Langerhans was not present, since the pressure of the contents of the cyst eventually must have thinned the walls of the dilated duct and caused atrophy of preexisting parenchyma.

Unfortunately the contents of the cyst were lost during operation, so that tests for evidence of pancreatic secretion, such as alkalinity, presence of albumin and power of digesting starch and coagulated egg albumin, could not be made.

SUMMARY

A case of embryonal cyst of the wall of the stomach which encroached on the pylorus and produced symptoms of pyloric obstruction is presented. Evidence that this cyst was of pancreatic duct origin is offered; it was obtained both by histologic studies of sections of the wall of the cyst and by a study of the literature on aberrant pancreatic tissue.

DIAPHRAGMATIC HERNIA IN THE NEWBORN

REVIEW OF THE LITERATURE AND REPORT OF A CASE

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SAMUEL J. HOFFMAN, M.D.

AND

JENNIE KANTOR AMTMAN, M.D.

CHICAGO

The mortality from congenital diaphragmatic hernia would be perceptibly reduced by earlier recognition of the condition and earlier operative intervention. This end could undoubtedly be accomplished by more frequent appearance of reports in the literature, since in diagnosis congenital diaphragmatic hernia is often overlooked. Harrington [1] claimed that the incidence of the condition is in direct proportion to the frequency with which it is thought of in making differential diagnosis. Keith [2] expressed the feeling that persons with diaphragmatic hernia might be more successfully operated on if the condition were recognized at birth. Grulee [3] stated that congenital diaphragmatic hernia should be considered more often when diagnoses are made, especially in many cases of supposed dextrocardia. Sudden deaths at birth should not always be attributed to an enlarged thymus or to congenital heart disease; they should be further investigated by autopsy.

Although the mortality and the morbidity for diaphragmatic hernia are higher than they should be, the relative incidence of this condition is in reality comparatively small. Giffin [4] found that up to 1912 only 15 of the entire 650 cases he studied were recognized during life, and of these only 6 were observed in children under 5 years of age. A

From the Department of Pediatrics of the University of Illinois and from the Cook County Hospital.

1. Harrington, S. W.: Diaphragmatic Hernia: Symptoms and Surgical Treatment in Sixty Cases, J. A. M. A. **101**:987 (Sept. 23) 1933.

2. Keith, A.: Remarks on Diaphragmatic Hernia, Brit. M. J. **2**:1297 (Oct. 29) 1910.

3. Grulee, C. G.: Hirschsprung's Disease, Internat. Clin. **2**:100, 1915.

4. Giffin, H. Z.: Diagnosis of Diaphragmatic Hernia, Ann. Surg. **55**:388, 1912.

5. Footnote deleted on proof.

review of the literature from 1912 to 1929 by Greenwald and Steiner [6] revealed several studies made on adults but only a few on children. They were able to collect reports of 81 cases in children up to 10 years of age, of which 25 were recognized during life. In a report published in May 1936, Truesdale,[7] after a thorough search of the literature, stated that comparatively few cases of congenital diaphragmatic hernia in children have been reported. Of 303 cases discovered, in 165 the condition was revealed at autopsy. Truesdale attributed the apparent rarity of the disease to difficulty of recognition rather than to infrequency of occurrence.[8] He found that only 22 patients under 10 years of age had been operated on before 1931, and that among these the mortality was 41 per cent. Orr and Neff,[9] reviewing the literature, found that 16 infants under 1 year of age had been operated on; they added their own case. In this group the death rate was 47 per cent. Hedblom [10] found that in a series of 210 patients with congenital hernia under the age of 1 year, 75 per cent died before the end of the first month. It is apparent from these data that early operative intervention is a dire necessity in most cases.

Coryllos and Tow [11] reported a case of diaphragmatic hernia in a 13 day old infant in which they were able to repair the opening. This infant, they claimed, was the youngest on whom operation had been reported successful. It is the purpose of this paper to report another case of diaphragmatic hernia with successful surgical intervention in an infant 13 days of age and to stress again the importance of early diagnosis with consequent early operation.

EMBRYONIC DEVELOPMENT

The development of the diaphragm is usually summarized as follows: The septum transversum, extending dorsally from the ventral portion of the body wall, appears early in fetal life. The openings between the

6. Greenwald, H. M., and Steiner, M.: Diaphragmatic Hernia in Infancy and in Childhood, Am. J. Dis. Child. **38**:361 (Aug.) 1929.

7. Truesdale, P. E.: Diaphragmatic Hernia in a Child, Aged One Year, J. A. M. A. **96**:847 (March 14) 1931.

8. Truesdale, P. E.: Diaphragmatic Hernia: Varieties and Surgical Treatment of the Hiatus Type, Am. J. Surg. **32**:204 (May) 1936.

9. Orr, T. G., and Neff, F. C.: Diaphragmatic Hernia in Infants Under One Year of Age Treated by Operation, J. Thoracic Surg. **5**:434 (April) 1936.

10. Hedblom, C. A.: The Selective Surgical Treatment of Diaphragmatic Hernia, Ann. Surg. **94**:776 (Oct.) 1931.

11. Coryllos, P. N., and Tow, A.: Left Congenital Diaphragmatic Hernia, in Baby of Thirteen Days, Operated on Successfully, J. Thoracic Surg. **2**:56 (Oct.) 1932.

peritoneal and the pleural cavity close approximately at the sixth week of embryonic life, and muscular fibers begin to appear in the forming diaphragm. The last part of the diaphragm to close is the region at the site of the pleuroperitoneal canals, which are located in the dorsal walls of the body near the midline. In the normal diaphragm, areas of muscular deficiency, termed the foramina of Bochdalek, mark their positions on both sides. The foramina of Morgagni, through which pass the superior deep epigastric vessels occurring anteriorly on both sides of the sternum, are similar gaps.

Embryologic deficiency is commonly held accountable for congenital diaphragmatic hernia, which, according to most authors, usually occurs at the following sites:

1. Through the hiatus pleuroperitonealis (foramen of Bochdalek), which is a gap in the musculature covered by pleura and peritoneum, and which is found posteriorly at the junction of the lumbar and costal portions of the diaphragm.

2. Through the dome of the diaphragm (in cases of mild involvement not really a hernia but merely a bulging of part of the diaphragm known as "eventration").

3. Through the esophageal opening.

4. Through one of the foramina of Morgagni.

5. Through the gap left by the absence of the left half of the diaphragm, usually situated posteriorly.

Congenital diaphragmatic hernia is more common on the left side than on the right. The generally accepted reason is threefold: First, the diaphragm is supported by the mass of liver; second, the right crus is longer and thicker; third, there are two fibrous bands on the right side. About 90 per cent of the hernias in infants and children are without sacs. Bradley and associates [12] declared that congenital diaphragmatic hernia is twelve times more common on the left side than on the right.

The mechanism of diaphragmatic hernia was explained by Barrett and Wheaton [13] when they discussed a case in this fashion:

> . . . At birth very little, if any, of the intestines had passed through the orifice, but . . . as the child cried and breathed, the coils were sucked into the thorax until the pressure upon the lungs was such that life was no longer possible.

12. Bradley, W. N.; Zulich, J. D., and McKee, E. E.: Congenital Diaphragmatic Hernia: Preliminary Report of a Case, Arch. Pediat. **47**:384 (June) 1930.

13. Barrett, N. R., and Wheaton, C. E. W.: The Pathology, Diagnosis and Treatment of Congenital Diaphragmatic Hernia in Infants, Brit. J. Surg. **21**:420 (Jan.) 1934.

Once the intestines have passed into the thorax the negative pressure tends to prevent or hinder spontaneous reduction such as might occur under the influence of gravity. In a number of cases, however, the amount of bowel which has herniated is not in itself sufficient to influence the workings of the chest. . . . The trouble begins for the patient when, owing to an overloaded bowel or tightness of the hernial orifice, which presumably does not increase much in size as the infant grows, a state of gradually increasing distension of the gut occurs. This distension is followed by an upset in the peristalsis of the herniated bowel . . . paralytic ileus is gradually developing, during which [days] a diagnosis and treatment may be attempted; a longer delay leads to an increase of intrathoracic pressure which impedes the action of the heart and lungs and results in gangrene of the bowel.

SYMPTOMS AND TREATMENT

The symptoms of diaphragmatic hernia can be grouped chiefly under cyanosis and other disturbances in the cardiorespiratory mechanism; in older children there may be added vague dyspeptic symptoms. Cyanosis may come on suddenly or after eating, or it may be constant. The pressure of the herniated organs on the heart and the vessels, as well as the mechanical interference with the action of the lungs, no doubt accounts for the cyanosis. In addition to cyanosis and variable respiratory difficulties, there must be included difficulty in feeding, vomiting and loss of weight. Greenwald and Steiner [6] found cyanosis to be an outstanding symptom in 19 cases. Respiratory disturbances consist in failure to breathe spontaneously and consequent death at birth, and in feeble respiratory attempts and dyspnea. A peculiar weak cry has been mentioned by many. In infants over 1 month old and in older children, Harrington [1] remarked, the vague dyspeptic symptoms are not in proportion to the gravity of the lesion. That there is a relative paucity of observable symptoms in the newborn is also brought out in his review of 32 newborn infants, only 2 of which showed either tympany on percussion on the involved side, an absence of breath sounds, dulness on percussion on the uninvolved side, bulging of the thorax, gurgling sounds in the chest or retraction of the abdomen.

When there is any suspicion of diaphragmatic hernia because one or more of the aforementioned signs are present, recourse should be had to roentgen studies. A single weak peculiar cry immediately after delivery, unexplained cyanosis and dextrocardia were noted in a case reported by Schreiber.[14] Davis' [15] chief observations in an infant 8 days old were attacks of cyanosis and of dyspnea which were relieved by

14. Schreiber, G.: Case of Left Sided, False Diaphragmatic Hernia in New-Born Infant, Arch. de méd. d. enf. **25**:607 (Oct.) 1922.

15. Davis, C. M.: Diaphragmatic Hernia in New-Born, Am. J. Dis. Child. **24**:356 (Oct.) 1922.

holding the child upright. Clark's [16] report of a newborn infant included as symptoms cyanosis, a peculiar weak moaning cry, dyspnea and difficulty in nursing, with tympany on percussion on the left side of the chest, absence of breath sounds and constant gurgling sounds in the chest; a roentgenogram substantiated the diagnosis. The outstanding symptoms listed as evidence of obstruction by Orr and Neff in a review of a number of cases [9] were pain, dyspnea, cyanosis and vomiting. Diagnosis was always confirmed by roentgenograms. A history of

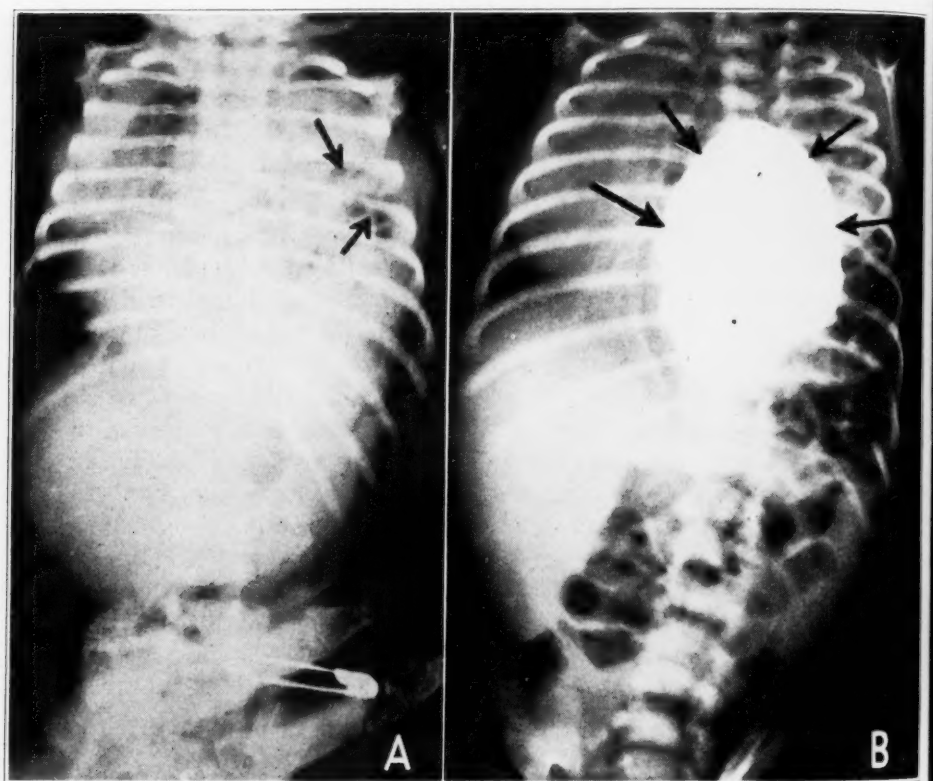

Fig. 1.—Roentgenograms taken, *A*, seven days after birth, showing how loops of bowel in chest displaced the lung and the heart, forcing them to the right; *B*, after a barium sulfate meal on the same day, showing the position of the stomach in the chest.

cyanosis, an increase in respiratory rate noted on the seventh day and an unnatural emptiness in the appearance of the abdomen led to a diagnosis in the case which these authors contributed. Their patient was successfully operated on on the twenty-seventh day.

16. Clark, J. D.: Diaphragmatic Hernia, Am. J. Obst. & Gynec. **8**:216 (Aug.) 1924.

In differential diagnosis of diaphragmatic hernia in the newborn, one must bear in mind all the conditions which can cause cyanosis, notably dextrocardia, congenital heart disease, congenital atelectasis, atresia of the esophagus, enlarged thymus and, in cases in which vomiting and loss of weight are present, pyloric stenosis.

The treatment, of course, is surgical. Barrett and Wheaton [13] stated that operative procedure is possible very early and is the only form of treatment when a portion of the intestine is in the thoracic cavity and certainly when signs of partial intestinal obstruction are present.

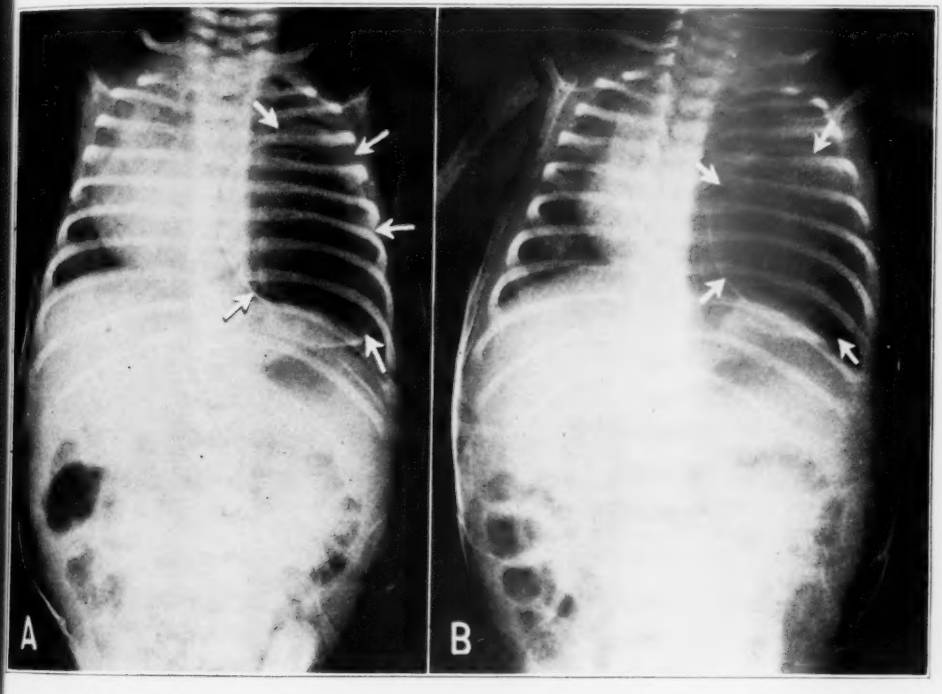

Fig. 2.—*A*, roentgenogram taken two hours after operation, showing the heart entirely to the right. The arrows indicate the sac. *B*, roentgenogram taken four days after the operation, showing the heart returning toward the left and diminution in the size of the sac.

REPORT OF CASE

M. A. E. was born Oct. 23, 1935, after normal labor and delivery. At birth the child had a jerky type of breathing; she became cyanotic after the intake of food. Vomiting occurred frequently, after which the cyanosis usually disappeared. Physical examination revealed a well nourished infant, weighing 7 pounds 11 ounces (3,487 Gm.), with a respiratory rate of 45. The chest seemed full, particularly on the left side, and the abdomen was scaphoid. Percussion of the chest anteriorly produced a tympanitic note over the left side and dulness over the right

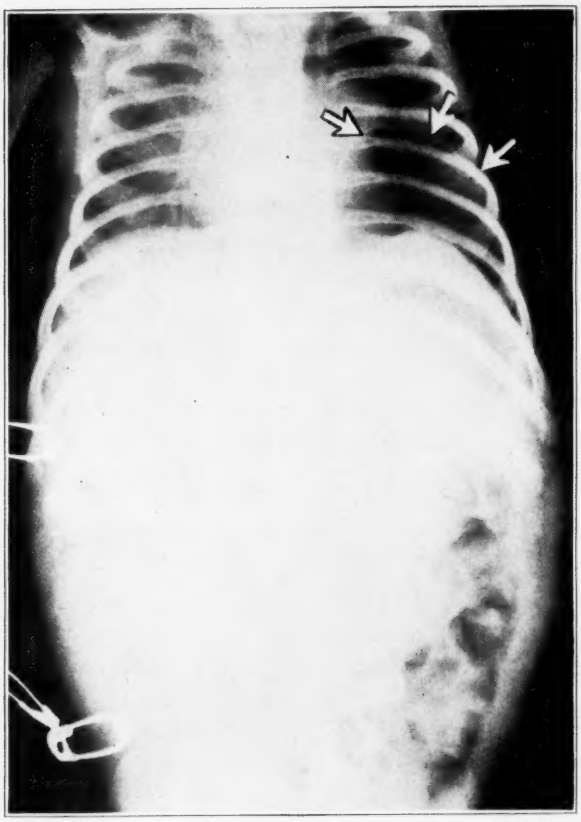

Fig. 3.—Further progress of the organs toward normal positions, as seen eight days after operation.

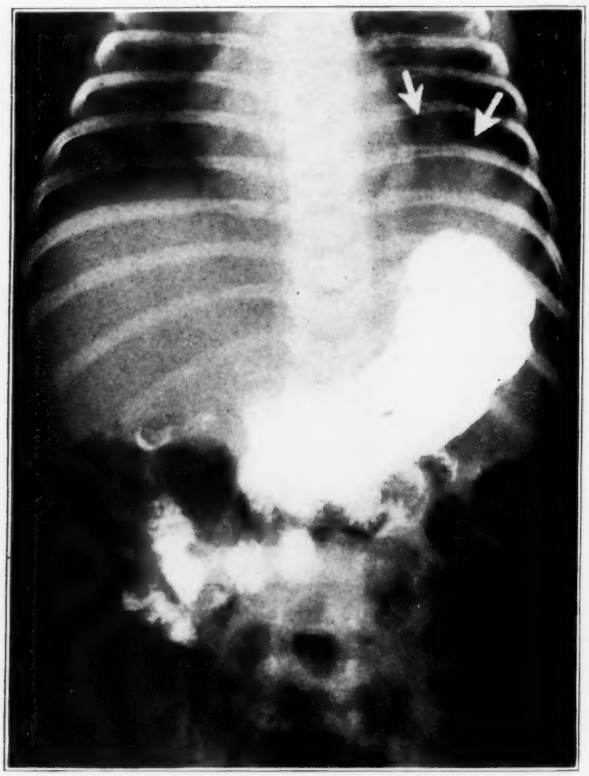

Fig. 4.—The stomach in the abdomen, as shown by a roentgenogram taken after a barium sulfate meal.

side. Posteriorly, on the left side there was slight impairment of resonance. On auscultation one could easily hear peristaltic sounds over the left anterior part of the chest and heart sounds on the right, beginning at the right axillary line. Posteriorly on the left side there was bronchial breathing, indicating compression atelectasis (fig. 1).

On November 6, thirteen days after birth, the child was operated on by one of us (K. A. M.). With the patient under ether, a left subcostal incision about 10 cm. in length was made, disclosing in the left side of the diaphragm an aperture 5 cm. in diameter, through which the stomach, the small bowel and part of the spleen had herniated. The abdominal viscera were withdrawn from the left pleural space. The opening of the diaphragm was closed with interrupted sutures of

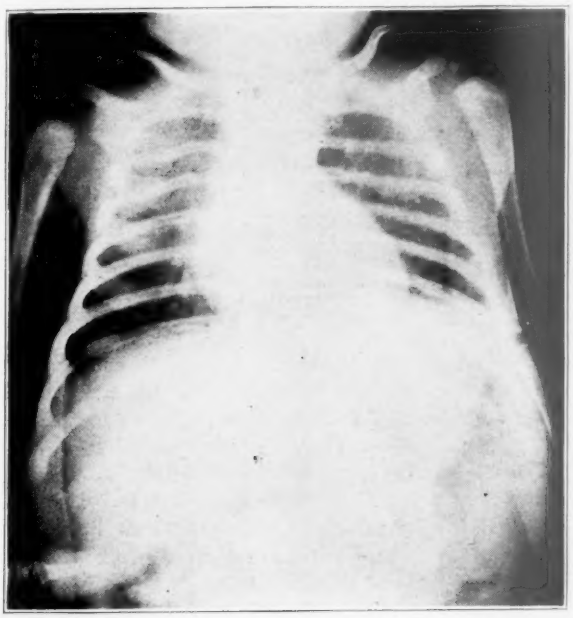

Fig. 5.—Roentgenogram showing the thoracic organs in normal position two months after operation.

black silk. Closure of the abdominal wall was accomplished by interrupted silk sutures with continuous silk in the skin.

The postoperative course was uneventful. The child was put on a diet of evaporated milk mixture and gained normally thereafter. Figures 2, 3 and 4 show the progressive return of the mediastinum and the lungs toward normal positions after absorption of the air from the hernial sac. Two months after the operation the position of the thoracic organs was completely normal (fig. 5).

SUMMARY

The literature on diaphragmatic hernia is reviewed, and stress is again placed on the importance of early diagnosis with timely surgical intervention. One of the earliest cases in which operation has been successful is reported.

DIFFUSE DILATATION OF THE PULMONARY ARTERY

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Dilatation of the conus and of the main trunk of the pulmonary artery is frequently associated with patent ductus arteriosus. Dilatation of the smaller branches of the pulmonary artery (diffuse dilatation) is a less frequent occurrence, and its clinical demonstration is a rarity, we believe. Further, diffuse pulmonary dilatation is referred to in reports of a varied group of conditions, many of which occur practically only in older patients.[1] One wonders whether diffuse pulmonary dilatation might not be more frequently seen if sought for systematically among large groups of children with congenital cardiac disease or with mitral stenosis.

REPORT OF A CASE

A boy was first seen in June 1926, when he was 3½ months of age. At that time he showed the characteristic signs of patent ductus arteriosus: a rough systolic murmur over the entire chest, a thrill extending into the neck and dulness on the left in the second and third interspaces, a sign described by Gerhardt as characteristic of pulmonary dilatation.

The boy has been under the continuous care of one of us since then. He is now 11½ years of age; his body is thin, narrow and undernourished, of a type rather characteristically associated with congenital heart disease. He has passed through the usual series of slight infections involving the upper respiratory tract and other infections; on one occasion, a year before the writing of this paper, he suffered from mild bronchopneumonia. At no time has he had symptoms suggestive of the rheumatic state. Cyanosis has been present from time to time. In general, however, he has had a high color, a flush rather than true cyanosis, except during exercise; then typical but mild purplish cyanosis has been observed in the ears, cheeks, lips and finger nails. At no time has there been congestion of the lungs or increase in size of the liver, typical evidence of congestive heart

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1. D'Aunoy, R., and Von Haam, E.: J. Path. & Bact. **38**:39, 1934. (This paper lists 87 cases of dilatation (aneurysm) of the pulmonary artery. It includes cases in which there were the most diverse lesions and varied causation. We believe that reclassification is advisable, but our limited clinical experience with the condition does not warrant our assuming the task.) Wessler, H., and Jaches, L.: Clinical Roentgenology of Diseases of the Chest, Troy, N. Y., The Southworth Company, 1923, p. 26. Pezzi, C.: The Radioscopic Sign of the "Hilum Dance," in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 3, p. 931.

failure. Recently questionable clubbing of the fingers has been noted. The pulse rate has been variable, at times being as high as 132 and at other times as low as 80. Percussion shows that the heart is enlarged, the apex extending to a point about 2 fingerbreadths to the left of the nipple line and the right border 2 fingerbreadths to the right of the sternal margin. Clinical and fluoroscopic studies indicate that the border of the heart extends somewhat farther to the right than is shown in the accompanying roentgenogram.

The murmurs are typical of patent ductus arteriosus. One murmur now suggests loud machinery; it is heard over the entire precordium but predominantly over the pulmonic area. It is audible also posteriorly. A thrill occupying the systole and part of the diastole is transmitted upward to the vessels of the neck; there is dulness in the second and third left interspaces. In April 1936 there was reduplication of the first and second sounds at the apex. It was difficult to determine whether this was independent or was transmitted from the pulmonic murmur. At present two murmurs are heard at the apex. The presystolic murmur is heard best just within the nipple line, is transmitted a few centimeters toward the axilla and extends almost to the sternal margin on the right. It is followed by an accentuated first sound. The systolic murmur is loud at the apex, becomes fainter toward the pulmonic area and is lost in the machine-like murmur in that region. It is also transmitted to the axilla and toward the sternum. These murmurs seem to be different in time from the loud pulmonic murmurs.

The boy has been seen at least three or four times a year and repeatedly has been examined by fluoroscopy. In December 1936 a striking and rather dramatic change was noted. In the upper hilar region of the right lung a definite pulsation was observed during each systole, and similar pulsations, though less striking and more diffuse, were noted in the lower hilar regions on the right. Further study confirmed this first observation and permitted more exact delineation. The pulsations are sudden and obvious and are more marked when the breath is held. The area of the upper one is about the size of a 25 cent piece. In the midhilar region pulsation of a smaller mass is visible, and just below it is seen a pulsation which is rather elongated and is directed toward the diaphragm. A relatively transparent area is noted in the anteroposterior position between these pulsating bodies and the cardiac shadow proper.

COMMENT

Necropsy in cases of congenital heart disease so frequently shows surprising and multiple lesions that it has become customary to avoid precise anatomic diagnosis. Indeed, we shall avoid analysis of symptoms and signs, except so far as such analysis may throw light on the problem of dilatation of the pulmonary artery. Thus it does not seem relevant to discuss the question as to whether this is a case of pure patent ductus arteriosus or whether it is associated with a patent interventricular septum or other congenital tract. The question of mitral stenosis is of more importance, in view of the fact that this lesion alone may frequently produce dilatation of the pulmonary artery. The characteristic apical murmur, which is independent of the murmur at the base, and the enlargement of the left auricle demonstrated by fluoroscopy are consistent with the belief that there is coexistent mitral valvulitis. The association of rheumatic infection or other cardiopathy with

congenital lesions is well known. Nevertheless, one cannot be absolutely certain in this case that mitral stenosis is present. When the heart is enlarged and distorted by one or more congenital lesions, one hesitates to ascribe to a pathologic mitral ring murmurs that otherwise might be considered characteristic of mitral stenosis. Too often under comparable circumstances necropsy has failed to show mitral stenosis when clinically the murmurs seemed typical of that condition. Further, there is no evidence of rheumatic disease in the case presented here. For these reasons, the diagnosis of mitral stenosis is made with certain mental reservations.

The causes of diffuse dilatation of the pulmonary artery are varied and numerous, as reviewed by Oppenheimer.[2] Discussion of the whole subject is not pertinent to our problem. It is sufficient to mention that the classification includes congenital and acquired lesions of the vessels, many of which are associated with hypertension of the lesser circulation. Our case falls into the group in which the condition is due to congenital vascular anomalies, with possibly an associated factor of rheumatic mitral valvulitis.

The pathogenesis of the type of dilatation under discussion depends on increased pressure in the pulmonary artery. The dynamics of the circulation in our case may be visualized as follows: At rest, the blood flows from the aorta through the ductus into the pulmonary artery. This arteriovenous shunt throws more work on the right side of the heart and induces a strain on the elasticity of the pulmonary artery and its branches. Exercise or any factor which induces an excessive pulmonic load in this child raises the pressure in the lesser circulation above that of the aorta and causes a venous-arterial shunt, effecting transitory cyanosis. The long-continued repetition of this process over a period of years leads to hypertrophy and dilatation of both ventricles. If the diagnosis of mitral stenosis is valid, there is additional cause for the high pressure within the lesser circulation. This increased pressure in the pulmonary vessels is the essential element in the pathogenesis of the lesion.

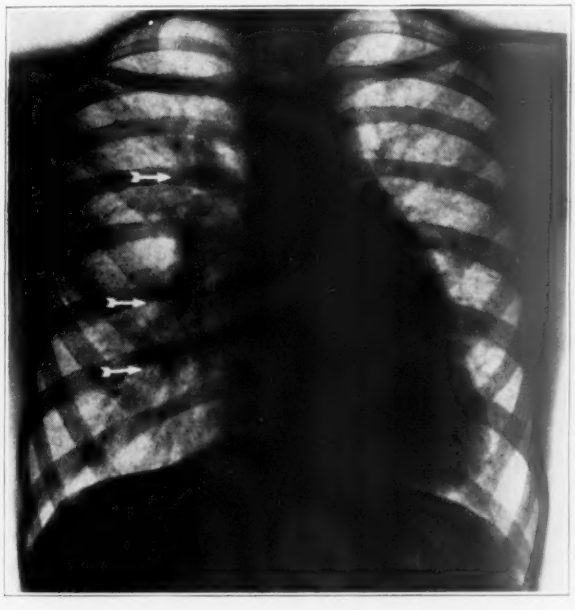
No relation can be established between the appearance of these pulsating hilar shadows and the clinical course of the disease. There is nothing to suggest that the child's condition has been worse since they were discovered.

Assmann[3] described pulsating hilar shadows and distinguished the true pulsation of the arteries (*Eigenpulsation*) from the pulsation

2. Oppenheimer, B. S.: Idiopathic Dilatation of the Pulmonary Artery, Tr. A. Am. Physicians **48**:290, 1933.

3. Assmann, H.: Die klinische Roentgendiagnostik der inneren Erkrankungen, ed. 5, Leipzig, F. C. W. Vogel, 1934, vol. 1, p. 168.

transmitted from the heart. A large heart beating violently may shake the mediastinum and the hilar regions and thus cause pulsation. The question may be raised as to whether the pulsations in our case are of primary vascular origin or are merely transmitted. The fluoroscopic evidence indicates definitely that they are due to pulsations of the pulmonary arteries themselves. The pulsating areas are discrete, and the remainder of the hilar regions shows no change. The roentgenogram reveals shadows far larger than normal in the exact position of the pulsating zones (figure).



Roentgenogram showing the areas of pulsation. The arrows indicate their position.

SUMMARY AND CONCLUSIONS

A case is reported of diffuse dilatation of the pulmonary artery due to a patent ductus arteriosus and possibly associated with (rheumatic) mitral valvulitis.

The recognition of this condition depends chiefly on fluoroscopy. Until the frequency of its occurrence can be established by repeated fluoroscopic examination of large groups of children in whom increased pressure in the pulmonary arteries justifiably may be suspected, the clinical significance of the condition will remain problematic.

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Progress in Pediatrics

A TALMUDIC CONTRIBUTION TO THE HISTORY OF DIPHTHERIA

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A Talmudic science of medicine analogous to the Galenic science, which would correspond to the Hindu or Greek system, does not exist. What one generally designates as such should more correctly be termed a compilation of the scattered remarks of Talmudic authors regarding medical matters. These remarks of the different authors were made solely for the purpose of forming a foundation for the Law. This was so because the Talmud [1] first of all was intended to lay down normal controls for all conditions of life (Halacha). It is true also that the Agoda contains occasional remarks on subjects from the field of medicine. In connection with this, one must remember that only a small number of the Talmudists were professional physicians and that the larger part of the reports therefore must be attributed to popular medical ideas. What remarks came from lay persons and what from physicians can be distinguished only in isolated cases. It therefore would be unjust if one should judge the Talmudic medical science by the criterion which is used in critical evaluation of purely medical documents of antiquity. That in spite of this a contribution to the history of medicine can be obtained from the Talmud will be shown by the following instance of a disease which is frequently mentioned in the Talmud.[1] At the same time one will become aware of the difficulties to be combated in a presentation of this nature, even though in the case discussed here they cannot be termed great.

The disease I refer to is termed the *askara* disease, better known today as diphtheria. To A. H. Israëls,[2] a physician in the Netherlands, is due the credit of first finding the mention of diphtheria in the Talmud [1] and of pointing to that passage of Aretaeus.[3]

From the Department of Obstetrics and Gynecology, University of California Medical School.

1. Schwab: Le talmud de Jerusalem, Paris, 1878-1889.

2. Israëls, A. H.: Dissertatio historico-medica exhibens collectanea gynæcologica ex talmude Babylonico, Groningen, P. van Zweeden, 1845.

3. Preuss, J.: Biblisch-talmudische Medizin: Beiträge zur Geschichte der Heilkunde und der Kultur überhaupt, Berlin, S. Karger, 1911; Allg. med. Centr.-Ztg., 1899, no. 76, pp. 2-15.

Of the old Talmudic commentators, Rabbi Jizchaki [1] (Raschi of Troyes, 1040 to 1105) translated the word *askara,* which according to his conception designates a manner of death, by "enstranglement" or "strangulation." As the name of a disease, he chose the designation *bun malan,* the interpretation of which has caused many difficulties. Under *askara* Raschi classified leprosy of the throat, which occasionally may produce the same symptoms as diphtheria and which physicians must have found frequently and concurrently with diphtheria.

The *askara* disease is mentioned often in the Talmud,[1] as in Taanith 3:4 it is stated: "A city in which an epidemic rages, fasts and sounds the trumpet." According to Rabbi Elasar, one also blows the trumpet in the surrounding townships. When does one speak of an epidemic? When in the town which furnishes 500 soldiers, 3 previously healthy human beings die of the same disease on three successive days.

To this is added in the Palestinian Talmud [1] (ed. Sitomir, fol. 14a): "It was taught that of *askara* already one case of death suffices" in order to make rules mandatory. In the Tosefta, and similarly in Taanith 19b, there is a passage which reads "In *askara* one blows the trumpet, if cases of death occur, not otherwise."

In the Palestinian Talmud,[1] Taanith 4:3 (fol. 19a), it is stated: "The God of the priests fasts every Wednesday on account of the children, so that *askara* will not come into their mouths." Further, it is stated in Berach 8a: "Thus it was taught 903 kinds of deaths have been brought into the world, the severest of all is *askara.* The death by *askara* appears like the pulling out of a thorn from wool flakes which lie amongst ferns."

In Sabbath 33a occurs the passage: "The punishment for evil speech is *askara.* In the vineyard of Babne one asks, 'Why does this disease begin in the intestine, and involve the mouth last?' The answer, because evil slander too comes out in this sequence, from the inside out."

In Berach 40a Rabbi Jochanan says: "Whoever gets used to eating lentils once in 30 days keeps *askara* away from his house, but it is not advisable to eat lentils every day. This may cause a fetid odor of the mouth.

"It was taught whoever after each meal does not partake of salt and after each beverage does not partake of water, he shall be apprehensive during the day on account of the odor from the mouth and during the night on account of *askara.*"

In Jebam 62b appears the report that 12,000 pairs of students of Rabbi Akiba from Gabbatha to Antipatris died between Easter and Pentecost of the same year of a bad disease because they did not esteem each other. According to Rabbi Nachman this disease was *askara.*

In Sotah 35a Rabbi Nachman states that scouts died of a plague which was *askara*. This incident is found also in Numbers 14:36 and 37.

In Pesach 105a one reads: "Whoever on Saturday evening before the evening prayer partakes of food dies of *askara*."

In Nidda 20a is seen this sentence: "Rabbi Ismeal berabbi Jose called down curses of *askara*." In Leviticus 11:18 to 20 it is declared: "You shall eat flesh . . . until you are nauseated." Resch Lakisch says: "until you suffocate from *askara*." It is probable that the disease mentioned under the name of *serunche* is also meant here.

In Jona 84a Rabbi Israel ben Rabbi Jose, about 150 A.D., says: "On the Sabbath one bleeds oneself." The opinions differ, however, because it is doubted whether bleeding was a remedy in this case.

In Kethub 30a Rabbi Joseph and Rabbi Chija state: "Even if the old tribunal does not exist its punishments still exist. Whoever deserves death by strangulation, either drowns in the river or dies of *serunche* or *askara*." In chapter 14 (fol. 60a) there is added, "or he is given into the hands of the Heathens who choke him to death."

From the passages and isolated remarks cited a definite picture of disease takes form.

Askara was an exceedingly dreaded epidemic disease, which chiefly affected children. It originated in the mouth and killed, after a severe death struggle, by means of suffocation. Of all the diseases known at the present time, this picture only fits diphtheria, especially diphtheritic croup.

Regarding the time of the citations, no absolute positive statements can be made. The fact that the first two citations were introduced by the formula "it was taught" permits one to infer a greater age. The truth will not be far away if all these assertions are placed in the second century after Christ.

That in fact diphtheria occurred at that time in the part of Syria neighboring Palestine is known from the much cited description of Aretaeus.[3] The comment that *askara* begins in the intestines and lastly involves the mouth finds its analogy in the theory of Aretaeus [3] unless one considers digestive disturbances, which precede diphtheria in the same manner as many other acute infectious diseases. According to Aretaeus this disease was caused by partaking of cold, rough things. If however these inner parts, such as the intestine and esophagus, became diseased, this disease was transmitted through spitting to the throat, tonsils and other surrounding tissues. The main difficulty of the entire problem of diphtheria was that of therapy. Whether venesection was a remedy or not caused many disputes, not only among the rabbis but

among all physicians of antiquity, from Hippocrates [4] on. The lentils which Rabbi Jochanan recommended as a prophylatic have disappeared from modern therapy. They played, however, a great role in the dietetics and therapy of antiquity.

Galen, Dioscorides and Plinius dedicated special chapters to their discussion.[4] The gargle which Aretaeus [3] recommended for angina contained, among other ingredients, a decoction of lentils. Plinius [4] also reported that the juice of cooked lentils was employed in cases of ulceration of the mouth. All of these authors discussed the subject and the effects of partaking of an excessive amount of lentils.

The regulation regarding the blowing of the trumpets, in addition to fulfilling the purely religious purpose, also served the eminently practical purpose of bringing to the attention of the citizenry the existence of an epidemic and the necessity of precautionary measures. The blowing of the trumpet must be compared to our modern issuing of bulletins and enforcement of quarantine.

SUMMARY

I have described a disease which, I feel, according to Talmudic citations, closely resembled diphtheria and in all probability was diphtheria.

It is interesting to note that the disease was described in the second century after Christ.

A. H. Israëls, a physician in the Netherlands, was the first to discover the picture of this disease in the Talmud.

350 Post Street.

4. Stone, I. S.: A Syllabus of the History of Obstetrics and Gynecology, Internat. Clin. **2**:266, 1918.

CARCINOMA OF THE THYROID GLAND IN CHILDREN

REPORT OF A CASE ASSOCIATED WITH MULTIPLE ANOMALIES OF DEVELOPMENT, WITH STUDIES OF BASAL METABOLISM, SERUM CHOLESTEROL AND CREATINE EXCRETION AFTER THYROIDECTOMY

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Carcinoma of the thyroid gland is rare in children. Hare [1] reported that in 15,000 thyroid glands operated on at the Lahey Clinic there were 258 instances, or 1.7 per cent, of primary malignant tumor of the gland; 6 of the tumors occurred in children under 14 years of age. Kennedy,[2] reporting from the Mayo Clinic, estimated that about 1 per cent of carcinomas of the thyroid gland affect children.

The following report describes the case of a 4 year old girl who in addition to the carcinoma of the thyroid gland showed bilateral congenital dislocation of the hips, spina bifida of the first sacral segment and small shadows of calcium density scattered throughout the cerebrum, as well as retinal lesions.

Laboratory studies of the child made after thyroidectomy added points of interest. After the surgical removal of the thyroid gland such children offer problems similar to those encountered in patients suffering from congenital athyreosis. Laboratory studies of the patients whose athyreosis is due to operation and not to developmental causes may be used as controls in observing the metabolic changes of congenital myxedema and may serve to prove that these changes are really due to absence of the thyroid hormone and not to other congenital anomalies. As far

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From the Babies Hospital and the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University.

1. Hare, H. F.: Cancer of the Thyroid in Children, Radiology **28**:131, 1937. Cattell, R. B.: Carcinoma of Thyroid Origin in Children, S. Clin. North America **12**:813, 1932; cited by Hare.

2. Kennedy, R. L. J.: Carcinoma of the Thyroid in Children, J. Pediat. **7**: 631, 1935; Malignant Diseases of the Thyroid Gland, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 1, chap. 38, p. 42.

as we know, no detailed laboratory studies following thyroidectomy have been reported for any of the other children who weathered the operation successfully and survived a number of years.

REPORT OF CASE

Anita G. was admitted to the Babies Hospital on July 13, 1936, at the age of 4 years, because of a swelling in the neck. She was born in Brooklyn of German parents. Her family history was unimportant except for a striking incidence of congenital dislocation of the hip in the female members of her mother's family. This branch of the family came from the eastern part of Thuringia, which adjoins Saxony. The patient's maternal grandaunt had unilateral and her daughter bilateral dislocation of the hips. The patient had bilateral dislocation of the hips, the patient's mother dislocation of the right hip, the mother's sister bilateral dislocation and her daughter unilateral dislocation.

The patient was an only child, and there were no other pregnancies. Her birth was normal; the weight at birth was 6 pounds and 14 ounces (3,118 Gm.). Shortly after birth bilateral internal strabismus and nystagmus were noticed. Because of the persistent nystagmus a roentgenogram of the skull was taken at the age of 8 months. This showed peculiar shadows scattered throughout the skull. Thereupon a roentgen study of the rest of the body was undertaken, and this revealed an enlarged thymus and congenital dislocation of both hips. Roentgen therapy was given for the enlarged thymus; the child was a patient in the New York Orthopaedic Dispensary and Hospital from the age of 16 months to the age of 30 months for treatment of the dislocation of the hips.

It was stated that her physical and mental development progressed normally. She suffered no illnesses except frequent mild colds, one attack of tonsillitis and one of unilateral otitis media.

The mother said that a few months after the child's dismissal from the New York Orthopaedic Dispensary and Hospital, when she was about 3 years old, a small swelling was noticed in the region of the thyroid gland.

The patient was first seen by one of us in May 1936, when she was almost 4 years old, in the ophthalmologic clinic of the Manhattan Eye, Ear and Throat Hospital. Her parents sought advice about the nystagmus. A hard nodular swelling was found in the region of the thyroid gland, and firm, freely movable, nontender lymph nodes were noted in both anterior cervical regions; the largest of them measured about 2.5 cm. in diameter. A blood count showed nothing abnormal. The girl was referred to the Babies Hospital for biopsy of one of the cervical nodes.

On admission to the Babies Hospital, at the age of 4 years (fig. 1), the patient appeared to be in fairly good general condition. She was alert, cooperative and in no apparent discomfort. She had no respiratory embarrassment or difficulty in swallowing, and there were no signs of hyperthyroidism. Her temperature, pulse rate and respiratory rate were normal. She weighed 14.4 Kg. (31 pounds and 10 ounces), and she was 100 cm. (39.37 inches) tall. The left lower extremity was 0.5 cm. shorter than the right, and the child walked with a slight limp on the left. On the outer aspects of both thighs, above the knees and below the left anterior superior iliac spine were well healed operative scars.

There were several hard nodular masses in the region of the thyroid gland and firm lymph nodes in both anterior cervical regions, varying in diameter from 0.5 to 2 cm. There was no generalized enlargement of the lymph nodes.

The eyes exhibited esotropia as well as nystagmus of the searching type. The optic disks showed waxy pallor, more marked in the temporal third. The eyes showed similar pathologic areas, each of which consisted of a sharply demarcated white atrophic patch overlaced with proliferated pigment and measuring about 1½ by 1 disk diameter. Both maculas were involved in the lesions. The impression of the optical consultant was that the alterations were due to central chorioretinitis with atrophy of the macular nerve bundle. He stated that this sharply defined, healed central choroiditis is usually ascribed to tuberculosis but that there was no adequate proof of a specific cause in this patient. He ascribed the nystagmus to the macular defects and attributed to it no other significance. He assigned the esotropia to excessive convergence associated with hypermetropia secondary to paresis of the superior rectus muscle.

Fig. 1.—A. G. at the time of admission to the hospital, showing esotropia and the mass in the thyroid region.

The throat appeared normal and the tonsils small and not inflamed. The heart, lungs and abdomen revealed nothing abnormal.

Roentgen examination of the skull showed multiple short linear shadows of calcium density scattered throughout the region of the cerebrum, without involvement of the structures in the posterior fossa. The cerebellum appeared to be free of these lesions (fig. 2).

The pelvis showed changes in the ossification centers in the proximal epiphyses of both femurs compatible with osteochondritis deformans juvenilis (Perthes' disease: flattening, irregularity in density and no evidence of destruction of the articular cartilages). There was spina bifida of the first sacral segment.

Preoperative roentgen study of the thorax showed no evidence of substernal thyroid or other mediastinal masses. The pulmonary fields were clear. The long bones showed no evidence of metastases.

The initial laboratory examination of the blood showed a hemoglobin content of 13.8 Gm. (95 per cent) and 4,500,000 red cells per cubic millimeter. The white cell count was 10,100, with 85 per cent polymorphonuclear cells, 12 per cent lymphocytes, 2 per cent mononuclears and 1 per cent eosinophils. The platelets numbered 395,000. The erythrocyte sedimentation rate was 8 mm. in one-half hour and 19 mm. in one hour (Westergren). The urine was normal. The calcium content of the serum was 9.8 mg. and the inorganic phosphorus content 3.4 mg. per hundred cubic centimeters. The serum cholesterol and the basal metabolic rate will be discussed later in this paper, in connection with other observations relating to thyroid activity. The Mantoux reaction (0.1 mg. of tuberculin) and the Kahn reaction of the serum were negative.

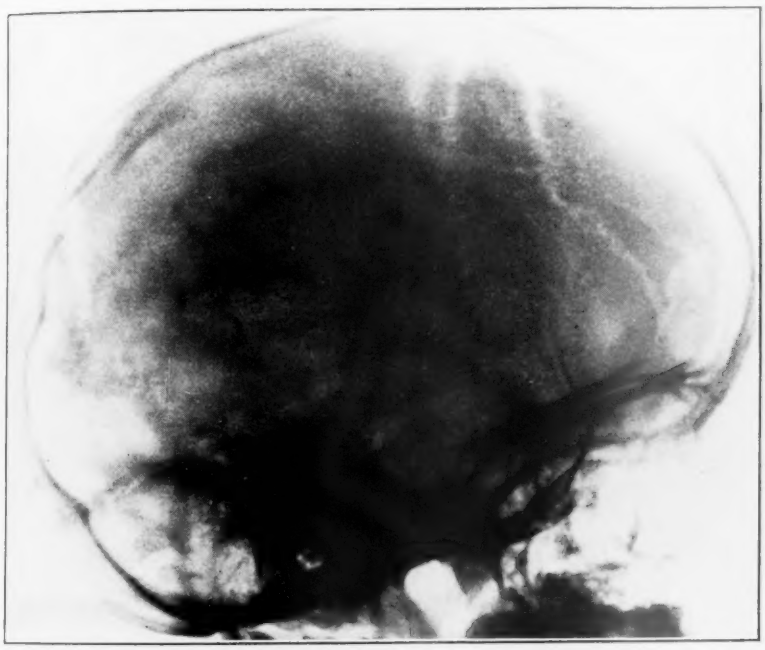

Fig. 2.—Roentgenogram of the skull, showing multiple small areas of calcium density scattered throughout the cerebrum.

Shortly after the patient's admission to the Babies Hospital a biopsy of a superficial cervical node was done. The pathologic report follows:

"The node (fig. 3) measured 15 by 13 by 9 mm. and was brownish red. On section a small translucent gray area was noted in the center.

"Microscopic examination showed that the lymphoid tissue was replaced by wide sheets of epithelial cells with large pale vesicular nuclei and indistinct cell margins. In places the cells formed acini lined by cuboidal epithelium and containing varying amounts of colloid. They resembled normal thyroid follicles. In some of these cysts the epithelium formed papillary projections into the lumen. Occasional mitotic figures were observed. The stroma was delicate, and the Foote-Bielschowsky stain showed that the reticulum surrounded groups of cells rather

than individual cells. The adjacent lymphatics and several small veins were filled with tumor cells (fig. 4).

"The diagnosis was metastatic carcinoma of the thyroid in the cervical lymph nodes."

Consultation with the departments of radiotherapy and surgery resulted in the opinion that the wisest procedure would be thyroidectomy with radical dissection of the cervical lymph nodes, followed by extensive roentgen therapy; this decision was dictated by the age of the patient, her good general condition and the absence

Fig. 3.—Photomicrograph of a section from a cervical lymph node, showing that lymphoid tissue has been replaced by masses of tumor cells. Note also acini containing colloid.

of distant metastases. Accordingly radical dissection of the cervical lymph nodes on the right side was done by Drs. J. M. Hanford and L. W. Sloan, of the Presbyterian Hospital, followed in two weeks by the same procedure on the left side. Finally, two weeks after this operation, total thyroidectomy was performed. It was noted at the time of the operation that the entire gland appeared involved by the carcinoma. It was moderately enlarged, firm and adherent to the trachea.

After each dissection 200 cc. of citrated blood was given by a transfusion. After each stage of the operation extensive edema of the head and face developed:

this was undoubtedly due to interference with the circulation, since both internal and external jugular veins were severed. However, the patient stood the procedures remarkably well and, except for brief rises in temperature to 101 F. on the day following each operation, remained afebrile.

Pathologic examination of the masses of lymph nodes removed from both cervical regions showed findings similar to those previously described. A portion of the jugular vein was present in each specimen.

The specimen of the thyroid gland (fig. 5) consisted of a hard crescent-shaped mass which was finely granular and encapsulated; it measured 5 cm. in transverse diameter, 4 cm. in vertical diameter and 2 cm. in thickness. On the anterior aspect there were several small discrete nodules. Microscopic examination showed large islands of tumor tissue separated by broad fibrous bands. Follicles which appeared normal were seen in the fibrous tissue. The major portion of the tumor was

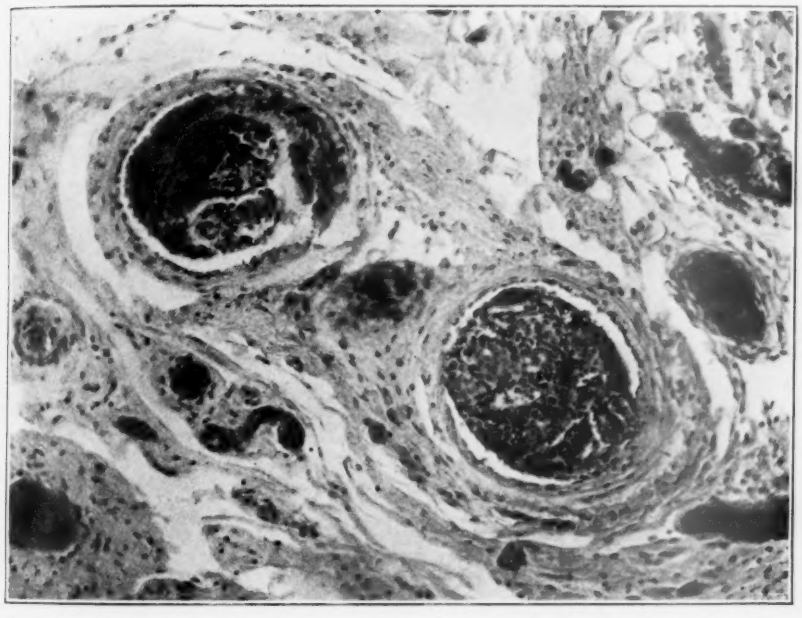

Fig. 4.—Small veins, adjacent to a cervical lymph node, filled with tumor cells.

composed of large solid masses of pale cuboidal cells with round pale nuclei, each of which had a single large nucleolus. The diagnosis was carcinoma of the thyroid.

A long series of roentgen treatments was given on each side of the neck after the thyroidectomy; 1,500 roentgens was administered on the left and 1,200 roentgen units on the right in the course of six weeks. About two months after the last treatment two small lymph nodes were felt just above the inner margin of each clavicle. As these areas had not been previously irradiated, they were subjected to a course of treatment; at the end of this the lymph nodes were no longer palpable.

Thyroid medication was instituted immediately after operation. Desiccated thyroid gland was used; the preparation employed[3] was stated to contain 0.3 per cent of organic iodine. The dose was varied between ½ and 1½ grains (30

3. Parke-Davis desiccated thyroid.

to 90 mg.) daily, depending on the clinical condition of the child and the results of laboratory examinations. In the beginning 1½ grains (90 mg.) was given daily; the child became excitable and had night terrors. Later on the daily dose was kept as low as was consistent with normal physical growth and mental development; it ranged from ½ to 1 grain (30 to 60 mg.) daily.

The child progressed remarkably well when given these low doses. She suffered a greenstick fracture of the right forearm from trauma which might be regarded as proportional to the lesion produced; this healed without delay. Except for chickenpox, she was healthy throughout the period of postoperative observation.

Fig. 5.—Photomicrograph of the thyroid gland, showing islands of tumor tissue separated by broad fibrous bands.

The child was recently (March 20 to 26, 1938) readmitted to the Babies Hospital, at the age of 5½ years (fig. 6), three years after the first swelling in the region of the thyroid gland had been noted and twenty months after thyroidectomy. She was in good general condition. The only manifestation that suggested hypothyroidism was slight dryness of the skin. Her appearance was somewhat disfigured by rather prominent superficial veins about the forehead, the lower portion of the left side of the face and both sides and the front of the neck and shoulders. The operative scars were smooth, well healed and inconspicuous. Both sternocleidomastoid muscles showed pronounced atrophy, and the

trapezius muscles were partially atrophic. No thyroid tissue could be felt. The eyes were practically unchanged. Examination of the chest and abdomen did not reveal any pathologic changes.

Laboratory examination of the blood showed a hemoglobin content of 14.8 Gm. (102 per cent) and 5,120,000 red cells per cubic millimeter. The white cell count was 8,450, with 74 per cent polymorphonuclear cells, 19 per cent lymphocytes, 6 per cent mononuclears and 1 per cent eosinophils. The erythrocyte sedimentation rate was 3 mm. in one-half hour and 8 mm. in one hour.

The calcium content of the serum was 9.8 mg. and the inorganic phosphorus content 3.4 mg. per hundred cubic centimeters.

The Mantoux reaction (0.1 mg of tuberculin) was again negative.

Roentgenograms of the skull and pelvis showed the pathologic findings observed on the first admission; there was no progress of these lesions. Roentgenograms

Fig. 6.—A. G. two years after operation.

of the long bones showed no evidence of metastases. The pulmonary fields and the heart were normal.

The data relating to growth and development have been summarized and are illustrated in figure 7.

Height and weight were compared with the averages given by Baldwin and Wood.[4] The line representing growth in stature nearly coincides with the normal curve. The child was about 3 pounds (1.3 Kg.) underweight when she came under observation, and she lost more weight during the period when the biopsy and the three operations were performed. She regained this loss of weight after discharge, and the rate of increase in weight was normal during the following year;

4. Baldwin, B. T., and Wood, T. D.: Weight-Height-Age Tables, New York, American Child Health Association, 1920.

she remained a few pounds below the average for her age. Osseous development, as measured by assessment of roentgenograms of the wrist and hand, was normal at the time of the girl's admission. Skeletal maturation progressed normally after thyroidectomy, so that twenty months later the skeletal age and the chronologic age were still equal. The child consistently produced the impression of being bright and mentally alert, an impression corroborated by the results of two psychometric examinations: Her intelligence quotient was 99 in January 1937 and 104 in March 1938. On both occasions the examining psychologist stated that her actual ability was probably higher than the numerical result of the test indicated, as she was handicapped by her defective eyesight and by using both English and German expressions in the verbal aspects of the examination (German is the language spoken in her home).

This satisfactory progress during the twenty months after thyroidectomy was obtained with a dose of thyroid smaller than that which is ordinarily used for

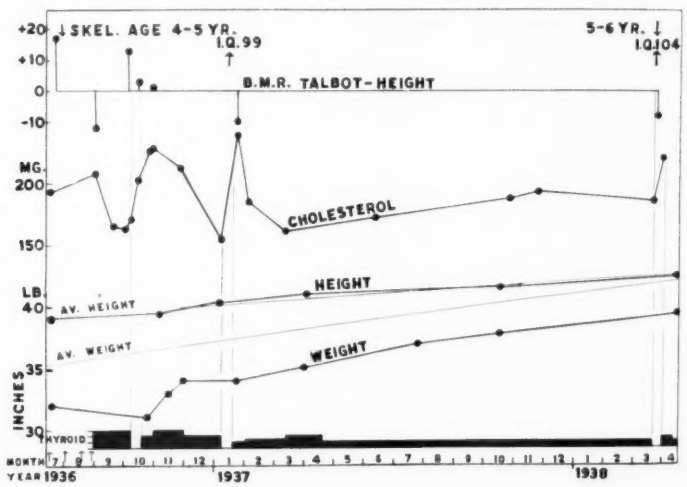

Fig. 7.—A. G.'s course during an observation period of 22 months. The passage of time is indicated from left to right and the individual clinical and laboratory items from below upward. The four arrows at the bottom (July and August 1936) indicate the biopsy and three operations. The black areas denote thyroid medication in ½ grain (0.03 Gm.) units. The interrupted vertical lines have been drawn to show more clearly the relation of withdrawal of thyroid to changes in the cholesterol level. *B. M. R. Talbot-Height* indicates basal metabolic rate compared with figures given by Talbot for girls of the same height; *Skel. Age* indicates skeletal age, and *I.Q.*, intelligence quotient. Cholesterol values are given as milligrams per hundred cubic centimeters of serum.

congenital athyreosis. Neither clinical scrutiny nor repeated roentgen examination of the lungs and skeleton has demonstrated recurrence of metastasis of the thyroid tumor which might supply additional thyroid hormone. In addition, laboratory studies have shown that the values of serum cholesterol and of urinary creatine fluctuate in the manner characteristic of hypothyroid children.

For these studies thyroid medication was interrupted three times, for periods varying from four to fourteen days. The figures and their interpretation will be taken up in detail in the comment.

METHOD

All determinations of cholesterol were carried out on blood serum by the method described by Schoenheimer and Sperry.[5] For the study of creatine excretion, a diet free of meat but containing milk and eggs was given during the four days preceding the collection of the first specimen of urine. The urine was kept in the ice box under toluene until collection of the twenty-four hour specimen was completed. The determinations were done soon afterward to avoid spontaneous conversion of creatine into creatinine. A modification of Folin's method[6] was used. The specimens were hydrolyzed in an electric oven at 110 C. for two hours instead of in an autoclave at 120 C. for twenty minutes. The results obtained in specimens treated in both ways showed close agreement. The final readings were made in a photoelectric colorimeter. The amount of creatine was recorded as the difference between total and preformed creatinine without conversion of the values of creatinine to those of creatine.

COMMENT

A survey of the literature discloses a number of reports of carcinoma of the thyroid gland in children in American and British medical journals but a surprising lack in the Continental periodicals. This lack is astonishing, since carcinoma of the thyroid gland has been reported as relatively common in mountainous countries where goiter is endemic (Haas[7]), and one would suppose that the child population would also show a higher incidence in these countries. All told, we have reviewed the reports of 20 instances of carcinoma of the thyroid gland in children under 15 years of age. With the case reported here, they are listed in table 1. The largest series is that of Kennedy,[2] consisting of 8 cases of carcinoma in children under 14 years of age, reported from the Lahey Clinic. One of the patients, in whom a tumor of the neck was first noticed at the age of 2 years, lived until the age of 30 years. Hare[1] reported 6 cases from the Mayo Clinic. Potter and Morris[8] described 5 cases, but we have included only 1 of these in our list as it was the only 1 of the 5 in which the patient's age was below 15 years, although in 3 others nodules were noticed in the thyroid region before that age was reached.

Table 1 reveals a striking preponderance of girls with the disease, there being 18 girls and only 3 boys. Pemberton[9] in his series of 457

5. Schoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745, 1934.

6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 603.

7. Haas, A.: Observations on Malignant Disease of the Thyroid Gland, Lancet **1**:1155, 1937.

8. Potter, E. B., and Morris, W. R.: Carcinoma of the Thyroid Gland: Report of Five Cases in Young Individuals, Am. J. Surg. **27**:547, 1935.

9. Pemberton, J. de J.: Malignant Disease of the Thyroid Gland, Ann. Surg. **87**:369, 1928.

TABLE 1.—*Cases of Carcinoma of the Thyroid Gland in Children*

Case No.	Author and Date of Report	Sex	Age When First Examined, Years	Age at Onset, Years	Type of Carcinoma	Treatment	Duration of Life: After Onset	Duration of Life: After Operation	Condition at Time of Report
1	Hughes, B.: Brit. M. J. **1**: 362, 1920....	F	13	10	Papilliferous carcinoma	Subtotal thyroidectomy	3 yr. 3 mo.	3 mo.	Living and well
2	Schultz,[17] 1926.....	F	5½	?	Carcinoma	Thyroidectomy and roentgen therapy	?	19 mo.	Living and well
3	Moncrieff, A.: Proc. Roy. Soc. Med. **23**: 109, 1929	F	11	4	Malignant goiter	Thyroidectomy	7 yr.	12 hr.	Died
4	Lee, F. C.: J. M. A. Georgia **23**: 123, 1934	F	8	7 yr. 10 mo.	Papillary adenocarcinoma	Subtotal thyroidectomy	3 mo.	.....	Living and well
5	Taylor and Wilkinson,[15] 1935.....	F	6¼	?	Papillary carcinoma	Too advanced for operation; metastases in lungs	?	.....	Died of asphyxia 6 wk. after admission
6	Potter and Morris,[8] 1935.....	F	14	11	Adenocarcinoma	Subtotal thyroidectomy and roentgen therapy	6 yr.	3 yr.	Living and well
7	Kennedy,[2] 1935	F	12	2	Papillary adenocarcinoma	Thyroidectomy at 12 yr., at 16 yr. and at 22 yr.	28 yr.	8 yr. after last operation	Died
8	Kennedy,[2] 1935	F	8	5	Papillary carcinoma	Subtotal thyroidectomy and radium therapy	14 yr.	6½ yr.	Living and well
9	Kennedy,[2] 1935	F	9	3	Adenocarcinoma	Subtotal thyroidectomy, radium therapy and thyroid	15 yr.	9 yr.	Living, fairly well
10	Kennedy,[2] 1935	F	7	6	Adenocarcinoma	Subtotal thyroidectomy and radium therapy	9 yr.	8 yr.	Living and well
11	Kennedy,[2] 1935	M	14	12	Multicentric adenocarcinoma	Subtotal thyroidectomy	7 yr.	5 yr.	Living and well
12	Kennedy,[2] 1935	F	13	7	Papillary adenocarcinoma	Roentgen therapy	8 yr.	.....	Living, fairly well
13	Kennedy,[2] 1935	F	8	7 yr. 8 mo.	Carcinoma	Roentgen therapy	9 mo.	.....	Living and well
14	Kennedy,[2] 1935	F	7	4½	Papillary adenocarcinoma	Subtotal thyroidectomy and radium therapy	3 yr.	3 mo.	Living and well
15	Hare,[1] 1937	M	6	5 yr. 11 mo.	Adenocarcinoma	Resection of thyroglossal cyst; second resection	3 yr.	3 yr.	Living and well
16	Hare,[1] 1937	F	11	9½	Papillary adenocarcinoma	Radical resection and roentgen therapy	7½ yr.	6 yr.	Living and well
17	Hare,[1] 1937	F	8	7	Adenocarcinoma	Subtotal thyroidectomy; roentgen and radium therapy	2 yr.	1 yr.	Living and well
18	Hare,[1] 1937	F	13	12½	Papillary adenocarcinoma	Subtotal thyroidectomy and roentgen therapy	1½ yr.	1 yr.	Living and well
19	Hare,[1] 1937	M	13	12¾	Carcinoma, small cell type	Tracheotomy and roentgen therapy	17 mo.	.....	Died
20	Hare,[1] 1937	F	9	8 yr. 10 mo.	Carcinoma simplex, small cell type	Excision of cervical glands; roentgen therapy	2 yr.	2 yr.	Living and well
21	Lemmon and Wyatt, 1938	F	4	4	Carcinoma	Total thyroidectomy [illegible]	3 yr.	3 yr.	Living and well

cases of malignant disease of the thyroid, which included 8 in which the patients were under 20 years of age, found that the disease was twice as frequent in females as in males.

The cause of carcinoma of the thyroid gland is unknown. According to Means,[10] the weight of evidence favors the view that carcinoma usually develops in a thyroid gland that is the site of a preexisting benign tumor, such as adenoma or fetal adenoma. Graham [11] stated the belief that at least 90 per cent of the malignant tumors of the thyroid arise in preexisting adenomas.

According to Dunhill,[12] classification of carcinoma of the thyroid varies in every country and with every author. One difficulty met with in trying to diagnose malignant growth at an early stage is that, apart from the scirrhous type, carcinoma rarely arises in a normal gland. From a pathologic standpoint Dunhill agrees with Wegelin [13] that the dividing line between nonmalignant and malignant tumors can probably nowhere be drawn with greater difficulty than in the cases of thyroid tumor. Graham [11] stated the opinion that invasion of the blood vessels is the most constant single indication of thyroid epithelial malignant growth.

Joll [14] classified primary thyroid carcinomas as (1) malignant adenoma, (2) papilliferous carcinoma and (3) carcinoma simplex. According to Taylor and Wilkinson,[15] most reported cases of the condition in children fall into the first two groups. Tumors of the adenomatous type are less malignant than those of the papilliferous type. Ewing [16] stated that the separation between adenocarcinoma and carcinoma of the thyroid is imperfect and that many transitional tumors are observed. Kennedy [2] found that the majority of thyroid neoplasms in children were adenocarcinomas of a low degree of malignancy. Schultz [17] also emphasized the relatively benign character of these tumors, although he stated that the histologic characteristics suggest high malignancy. Potter and Morris [8] concluded that the adenomas of the thyroid which they encoun-

10. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937, chap. 18, p. 477.

11. Graham, A.: Malignant Epithelial Tumors of the Thyroid, Surg., Gynec. & Obst. **39**:781, 1924.

12. Dunhill, T. P.: Carcinoma of the Thyroid Gland, Brit. J. Surg. **19**:83, 1931.

13. Wegelin, C., cited by Dunhill.[12]

14. Joll, C. A.: Diseases of the Thyroid Gland, London, William Heinemann, 1932, chap. 16, p. 299.

15. Taylor, A. B., and Wilkinson, B. M.: Carcinoma of the Thyroid Gland in Childhood, with Report of a Case, Arch. Dis. Childhood **10**:99, 1935.

16. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928, chap. 45, p. 942.

17. Schultz, O. T.: Tumors of Infancy and Childhood, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1926, vol. 8, chap. 193, p. 855.

tered in young persons represented benign congenital neoplasms rather than degenerative changes or involution bodies in an otherwise normally functioning thyroid. Joll [14] called attention to an unusual feature of malignant tumors of the thyroid which distinguishes them from malignant tumors of other glands, namely, their capacity under certain conditions to carry on the specific functions of the gland.

It is generally conceded that the clinical diagnosis of carcinoma of the thyroid gland is impossible in the early stages and that one must rely entirely on the pathologist. Constitutional symptoms are usually absent in the early period. An irregular firm nodular swelling of a part of the thyroid gland is generally the first abnormality noticed; on the other hand, the adjacent cervical nodes may be more prominent than the thyroid swelling. It is as a rule only later that hoarseness, difficulty in swallowing or embarrassment in breathing becomes manifest. Kennedy emphasized that "among children benign tumors of the thyroid gland have been found less frequently than have malignant tumors, and hence, any mass, however innocent appearing clinically, should be suspected of having malignant qualities." It is of interest that the parents of our patient sought medical advice for the ocular symptoms and were apparently not concerned about the small swellings in the child's neck.

Metastatic involvement, when it occurs, affects the following structures in this order of frequency: regional lymph nodes, lungs, thorax and mediastinum, and bones. In all cases in which malignant tumor of the thyroid is suspected, roentgenograms of the lungs and bones should be taken before surgical intervention is advised.

The prognosis in the individual case depends on a number of factors; these include the type of carcinoma, the stage of the disease, whether or not the growth is resectable, its radiosensitiveness and whether or not metastases are present. In general, carcinomas of the thyroid in children are of a low grade of malignancy and if seen in the early stages are amenable to treatment; therefore, the life expectancy is a matter of years rather than months.

Surgical intervention followed by roentgen therapy has proved the most satisfactory treatment (Hare and Swinton; [18] Pemberton [9]). Pemberton also advocated the surgical extirpation of benign adenoma of the thyroid, as it is frequently the precursor of carcinoma. Complete surgical removal of all of the involved lymph nodes is not always possible. In some cases in which such removal could not be effected prolonged courses of roentgen irradiation have had good therapeutic effect.

The other features of interest which our patient presented will be discussed briefly. In none of the previously reported cases of carcinoma of the thyroid gland were similar anomalies exhibited.

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18. Hare, H. F., and Swinton, N. W.: Cancer of the Thyroid, J. A. M. A. **110**:327 (Jan. 29) 1938.

The bilateral congenital dislocation of the hip in the patient and the high incidence of this deformity in the female members of the mother's family are worthy of note. Multiple incidence of congenital dislocation of the hip in a family would naturally suggest a hereditary factor. Gaugele,[19] from a study of this deformity which extended over thirty years, came to the conclusion that the determining factor is racial rather than hereditary. He found that in the regions of Germany originally settled by the Alamannic tribes congenital dislocation of the hip is rare, whereas in Saxony, Thuringia and Württemberg, regions that were overrun by the Slavs about 600 A. D., the deformity is singularly common. In 933 A. D. Henry the Fowler, the first Saxon king, conquered the Slavs and Germanized them, but "his reformation stopped at the pelvis." Zimmermann,[20] studying the patients with congenital dislocation of the hip who reported to the Munich Orthopedic Clinic, found that the majority of the patients or their parents came from the Bavarian East March or Franconia, whereas other orthopedic deformities did not show this geographic distribution. Whether consanguinity played a role is not mentioned. It is of interest to note that the family of our patient's mother came from Thuringia.

The multiple small linear shadows of calcium density scattered throughout the cranial vault also require explanation. Possibilities that suggest themselves include calcifying Cysticercus cellulosae and calcification in multiple angiomas or in minute cerebral hemorrhages possibly secondary to injury at birth. However, it is to be emphasized that the calcification was smaller and more linear than is usual with such conditions. When one attempts to explain both cerebral calcifications and retinal lesions on a single basis, the Hippel-Lindau syndrome suggests itself. This syndrome consists of angiomatosis of the retina associated with angiomas in the cerebrum or in the cerebellum (Hartmann and Sourdille[21]). Lindau found that angiomatosis of the retina is not always confined to the eye but is frequently an index of a systematic mesenchymal malformation which manifests itself in angiomatosis of the central nervous system (and of the retina) and is associated with multiple tumors and malformations in other organs (Karasek[22]). As

19. Gaugele, K.: Die Hüftgelenksverrenkung—eine Erbkrankheit? Zentralbl. f. Chir. **64**:983, 1937.

20. Zimmermann, M.: Die Heimat der Vorfahren der in München geborenen Kinder mit einer angeborenen Hüftgelenksverrenkung, München. med. Wchnschr. **82**:745, 1935.

21. Hartmann, E., and Sourdille, G.: Un cas de maladie de Lindau à deux: angiome du cervelet chez la mère, maladie de von Hippel chez le fils, Ann. d'ocul. **168**:881, 1931.

22. Karasek, O.: Angiomatosis retinae (von Hippel-Lindau), Klin. Monatsbl. f. Augenh. **95**:163, 1935.

Schieck [23] pointed out, the multiple character of the lesion is not a matter of metastasis from a primary tumor but probably represents multiple malformations which occur during embryonal development, in that mesodermal tissue grows into the nerve tissue as a heterotopic element and then undergoes pathologic proliferative changes.

Lindau is also responsible for the concept that in some cases angiomatous cysts of the cerebellum or angiomas in the region of the medulla oblongata or spinal cord are associated with cysts of the pancreas, with angiomatosis of the retina or with both (Putschar [24]).

Whether or not the retinal findings in our case could be interpreted as being of an angiomatous character is open to discussion. Some patients with angiomatosis of the retina, instead of showing red berry-like swellings or thick wormlike vessels, present degenerative manifestations of the retinal tissue, which give a whitish yellow appearance. As Schieck emphasized, the true nature of the disease becomes manifest when the patients who show angiomatosis of the retina succumb, as they frequently do, to tumor of the brain, especially to hemangioma of the central nervous system; death usually occurs late.

Bedell [25] and Karasek,[22] as well as Hartmann and Sourdille,[21] called attention to the familial character of this disease. As far as is known, there were no similar ocular lesions in other members of the patient's family.

In speaking of venous tumors of the brain Dyke [26] stated that they are most common in the occipital lobe and that when calcification occurs it is laid down in convoluted parallel streaks. However, in our patient the lesions were too widespread to suggest a tumor. Assmann's [27] descriptions of calcareous deposits within the skull do not conform exactly to the findings in our case, for he considered chiefly such localized shadows as may occur in psammoma, endothelioma, angioma, glioma and other tumors. He stated, however, that calcified tubercles give scattered shadows; in our case Mantoux reactions were repeatedly negative. Furthermore, these shadows of calcium density were discovered

23. Schieck, F.: Angiomatosis retinae (von Hippel Krankheit), in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 5, p. 603.

24. Putschar, W.: Ueber Angiomatosis des Zentralnervensystems und der Netzhaut (von Hippel-Lindau'sches Syndrom), mit besonderer Berücksichtigung der Pankreasveränderungen, München. med. Wchnschr. **82**:1084, 1935.

25. Bedell, A. J.: Angiomatosis of the Retina (von Hippel's Disease, Lindau's Disease), in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 777.

26. Dyke, C. G.: Diseases of the Skull and Intracranial Contents, in Golden, R.: Diagnostic Roentgenology, New York, Thomas Nelson & Sons, 1936, chap. 1, p. 11.

27. Assmann, H.: Gehirn und Schädel, in Die klinische Röntgendiagnostik der inneren Erkrankungen, ed. 5, Leipzig, F. C. W. Vogel, 1934, vol. 2, p. 1002.

when the child was only 8 months of age. For a further discussion of intracranial calcification and a more extensive bibliography the reader is referred to the article by Merritt, Faber and Bruch.[28]

The syndrome (if such it may be called) presented here was new to us. That a fetal adenoma and the retinal lesions as well as the cerebral calcification were present at birth is open to question, even though it seems probable. Whether these malformations can be explained on a single basis is also problematic. The congenital dislocation of the hips seemed to be an independent anomaly.

LABORATORY STUDIES DURING THE POSTOPERATIVE COURSE

The majority of children who have been operated on for carcinoma of the thyroid have survived. The further progress of these children is generally described as normal. Hare [1] mentioned that the level of the serum cholesterol remained within normal limits. No detailed studies of the athyroid state in these patients have been published.

Numerous clinical studies of the relation between thyroid activity, the basal metabolic rate and the values of serum cholesterol have been reported during the last fifteen years.[29] Although there is some divergence in the results obtained in cases of hyperthyroidism, the reports concerning hypothyroidism are uniform. In congenital [30] as well as in operative myxedema [31] hypothyroidism is associated with hypercholesteremia, a clinical observation which has been confirmed in animal experiments.[32]

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28. Merritt, K. K.; Faber, H. K., and Bruch, H.: Progressive Facial Hemiatrophy, J. Pediat. **10**:374, 1937.

29. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: The Relation of Cholesterol and Protein Deficiency to Basal Metabolism, Arch. Int. Med. **30**:563 (Nov.) 1922. Hurxthal, L. M.: Blood Cholesterol in Thyroid Diseases: Effect of Treatment, ibid. **52**:86 (July) 1933. Mason, R. L.; Hunt, H. M., and Hurxthal, L.: Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism: Their Significance, New England J. Med. **203**:1273, 1930.

30. Bronstein, I. P.: Studies in Cretinism: I. Blood Cholesterol, J. A. M. A. **100**:1661 (May 27) 1933. Schwarz, H., and Topper, A.: Cholesterol Partitions of the Blood in Myxedema (Cretinism), J. Pediat. **3**:242, 1933.

31. Gilligan, D. R.; Volk, M. C.; Davis, D., and Blumgart, H. L.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: Relationship Between Serum Cholesterol Values, Basal Metabolic Rate and Clinical Aspects of Hypothyroidism, Arch. Int. Med. **54**:746 (Nov.) 1934. Schnitker, M. T.; Van Raalte, L. H., and Cutler, E. C.: Effect of Total Thyroidectomy in Man: Laboratory Studies and Observations of Clinical Effects in Thirty-Nine Cases, ibid. **57**:875 (May) 1936.

32. Schmidt, L. H., and Hughes, H. B.: The Free and Total Cholesterol Content of Whole Blood and Plasma as Related to Experimental Variations in Thyroid Activity, Endocrinology **22**:474, 1938.

Normal values for the serum cholesterol obtained by the method employed in this study are available only for adults and infants,[33] not for children of the age of our patient. From our own unpublished observations on cretinism we can draw the conclusion that hypothyroid children progress satisfactorily when the cholesterol level remains between 150 and 200 mg. per hundred cubic centimeters of serum. The concentrations found for our patient during the whole period of observation are shown in figure 7 and, in their relation to changes in the basal metabolic rate and in urinary excretion of creatine, in figure 8.

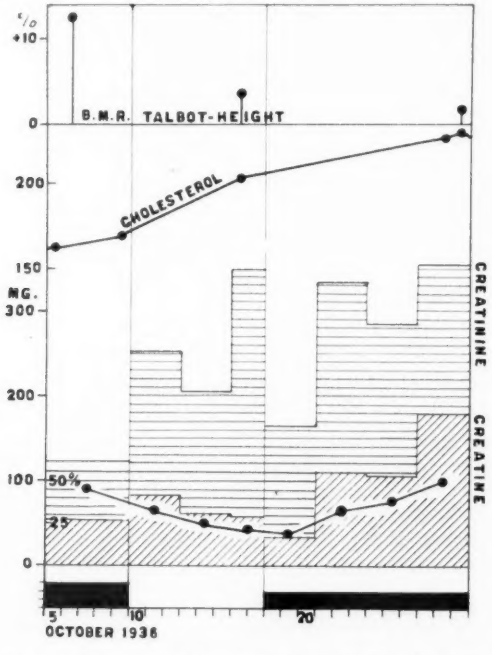

Fig. 8.—The effect of interruption and resumption of thyroid medication on A. G.'s excretion of creatine and creatinine, level of serum cholesterol and basal metabolic rate. Thyroid medication is indicated by the solid black areas at the bottom in ½ grain (0.03 Gm.) units. Values of creatine and creatinine are given as milligrams per twenty-four hour urinary excretion and of cholesterol as milligrams per hundred cubic centimeters of serum. The curve crossing the creatine area indicates the percentage of creatine in the total creatinine.

Only the figures for the total cholesterol content are given; the ratio of of combined to free cholesterol showed no significant variation from the normal average, ranging from 2.21 to 2.82.

33. Sperry, W. M.: Cholesterol of the Blood Plasma in the Neonatal Period, Am. J. Dis. Child. **51**:84 (Jan.) 1936; The Relationship Between Total and Free Cholesterol in Human Blood Serum, J. Biol. Chem. **114**:125, 1936; The Concentration of Total Cholesterol in the Blood Serum, ibid. **117**:391, 1937.

On the girl's admission to the hospital the cholesterol level was 194 mg. per hundred cubic centimeters of serum; the basal metabolic rate was elevated in comparison with the standards given by Talbot [34] for girls of the same height. Shortly after thyroidectomy the cholesterol concentration was slightly higher (208 mg.) and the basal metabolic rate markedly lower. The interval between the operation and this determination was so short that it is highly improbable that this depression indicated myxedema. It is more likely that the low rate reflected the immediate after-effects of the operation. During the first three weeks of thyroid medication the cholesterol value fell to 165 mg., and it remained at this level for the next three weeks, without any change in the daily dose. Six weeks after thyroidectomy medication was interrupted for one week. The cholesterol level rose significantly, and it continued to increase for about two weeks after treatment was resumed. The highest value recorded was 229 mg. After reaching this point the cholesterol content fell, and it was 154 mg. in January 1937. Thyroid was discontinued for another two weeks; again there was a conspicuous rise of the cholesterol level, which reached 240 mg. during the next three weeks, with a drop to 161 mg. in March. Determinations could not be made often enough to supply information concerning the rate of this drop. From April 1937 to March 1938 only ½ grain (30 mg.) of thyroid was given daily. The concentration of cholesterol rose slowly and then fluctuated around 190 mg. from October 1937 to March 1938. At this time thyroid was discontinued for four days only; the cholesterol value rose to 221 mg.

Several determinations of the basal metabolic rate were made during the entire period, but not frequently enough to be used for correlation with the fluctuation of the serum cholesterol.

This behavior of the cholesterol was in harmony with unpublished observations that we have made in approximately 10 cases of congenital hypothyroidism. We found the same rise after withdrawal of thyroid; this continued for some time after resumption of treatment and was followed by a slow fall, which lasted for several weeks thereafter. We give here some data on a child with cretinism who was studied at the same time under comparable experimental arrangements.

This girl, S. C., was a typical cretin. She developed well up to the age of 5 or 6 months and then showed conspicuous signs of progressive mental and physical retardation. She received some sort of treatment irregularly, the nature of which is not known. She had not received any medication for from six to eight months preceding our first observation. She was 8½ years old at that time, was 95 cm. (38 inches) tall (average height for her age, 122.5 cm. [49 inches]) and weighed

34. Talbot, F. B.; Wilson, E. B., and Worcester, J.: Standards of Basal Metabolism of Girls (New Data) and Their Use in Clinical Practice, J. Pediat. **7**:655, 1935.

18.2 Kg. (40 pounds). Osseous development was markedly retarded; her skeletal age was placed between 4 and 5 years. She walked insecurely, with a waddling gait. She was grossly retarded mentally and spoke only a few words, in a hoarse voice. Estimation of her mental age was not attempted until several months after treatment had been started. At that time her mental age was between 2 and 3 years. Toilet habits had not been established. She responded well to treatment with thyroid gland; the preparation used [35] had approximately one-fifth the potency of the preparation used for the child on whom operation was done. The dose ranged between 5 and 10 grains (300 and 600 mg.) daily. The girl grew nearly 5 cm. (2 inches) during the next two and a half months and lost some weight. There was a definite increase in the size of the ossification centers of the carpus. The patient's speech improved somewhat, and her gait became less clumsy and awkward. At that time, in October 1936, thyroid medication was interrupted for two weeks for a control study of these 2 different cases of thyroid deficiency.

Fluctuations of the basal metabolic rate, the level of serum cholesterol and the urinary excretion of creatine as influenced by thyroid medication and its withdrawal were studied in both cases. Up to the age of puberty the normal healthy child excretes considerable amounts of creatine in addition to creatinine.[36] This physiologic creatinuria is depressed in cases of hypothyroidism.[37] It can be restored to normal in a short time by thyroid medication. When the drug is discontinued or completely withheld the creatinuria will decrease or disappear entirely. In the case reported by Hess no creatine was excreted three days after thyroid was discontinued. In our own experience with several cretins, creatine never disappeared completely from the urine. Changes in excretion of creatine are thought to provide a more sensitive and rapid index of thyroid function than either the basal metabolic rate or the cholesterol content of the serum.

The main obstacle to the extensive use of the method lies in the circumstances that twenty-four hour specimens of urine are difficult to collect from young or mentally retarded children. It was not possible to secure complete twenty-four hour specimens throughout the period from either patient. To compensate for these accidental differences in the daily excretion, averages of from two to five day periods were

35. Burroughs Wellcome thyroid gland tabloid.

36. Hunter, A.: Creatine and Creatinine, New York, Longmans, Green & Company, 1928, p. 184. Harris, M. M., and Brand, E.: Metabolic and Therapeutic Studies in Myopathics, with Special Reference to Glycine Administration, J. A. M. A. **101**:1047 (Sept. 30) 1933. Marples, E., and Levine, S. Z.: Creatinuria of Infancy and Childhood: I. Normal Variations; Creatine Tolerance Tests and the Effect of Amino Acid in Normal Infants, Am. J. Dis. Child. **51**:30 (Jan.) 1936. Catherwood, R., and Stearns, G.: Creatine and Creatinine Excretion in Infancy, J. Biol. Chem. **119**:201, 1937.

37. Hess, J. H.: Blood Cholesterol and Creatine Excretion in the Urine as Aids to Diagnosis and Treatment of Hypothyroidism, Ann. Int. Med. **8**:607, 1935. Poncher, H. G.; Visscher, M. B., and Woodward, H.: Creatine Metabolism in Children with Hypothyroidism, J. A. M. A. **102**:1132 (April 7) 1934.

recorded (figs. 8 and 9), although determinations were done daily. The actual excretion of creatine and creatinine must have been higher than is represented in the charts. No attempt was made to determine the creatine tolerance.

Even these somewhat incomplete figures are of value in the study of hypothyroidism. Although creatine and creatinine are excreted independently, the ratio between these two substances thus varying in single specimens obtained at different times of the day, nevertheless there

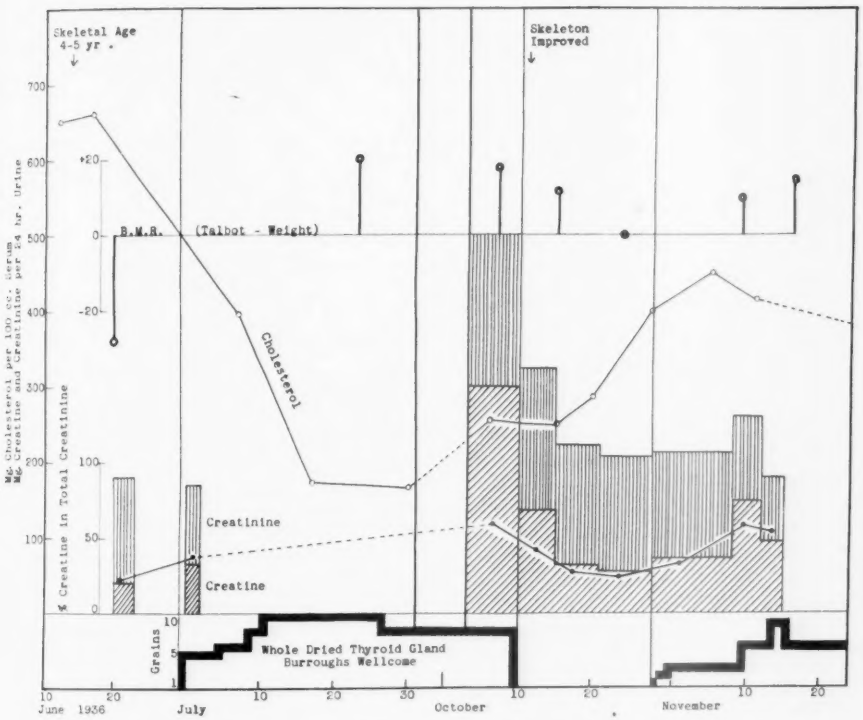

Fig. 9.—Two periods of observation of a cretin (S. C., aged 8 years), June 10 to July 30 and Oct. 1 to Nov. 27, 1936. Thyroid medication was given continuously during the interval. This chart illustrates the effect of thyroid medication and its withdrawal on the basal metabolic rate, the level of serum cholesterol and urinary excretion of creatine and creatinine.

exists a definite relation between the amounts excreted within twenty-four hours; this is demonstrable in mixed twenty-four hour specimens, even though they are incomplete. We have expressed it as the percentage of creatine in the total creatinine, which is the sum of creatine and creatinine. When the two substances are excreted in equal amounts, the creatine represents 50 per cent of the total creatinine. When excretion of creatine decreases while that of creatinine remains more or less con-

stant, as is the case with hypothyroidism, the percentage of creatine diminishes; when no creatine is excreted the percentage is zero. This relation appears to be of significance in evaluating the state of thyroid activity. Simply recording whether or not creatine is being excreted is insufficient, since creatine frequently decreases only and does not disappear entirely from the urine of cretins. The usefulness of this calculation, which allows one to determine creatinuria even in cases in which a complete collection of urine is not possible, has not been brought out in the previous publications dealing with excretion of creatine in hypothyroidism.

Figure 8 illustrates the findings for the child on whom operation was done. During the first five days she received thyroid in the same amount as during the preceding six weeks. She excreted 55 mg. of creatine and 67 mg. of creatinine per day. We are at a loss to explain these unusually small amounts. Though we encountered some difficulty in collecting the specimens of urine, the recorded loss in no instance approached 50 per cent. During the later periods of the experiment the amounts of creatine and creatinine excreted were more in agreement with values which one would expect for a girl of the patient's age. Creatine constituted 45 per cent of the total creatinine, as one would anticipate in a child receiving thyroid medication. After thyroid was discontinued, the percentage of creatine in total creatinine decreased progressively. It was 33 per cent during the first three days, 30 per cent from the fourth to the sixth day and 27 per cent on the seventh and the eighth day after withdrawal of thyroid. It continued to drop for three more days after treatment was resumed and reached a low point of 21 per cent. The creatine excretion rose during the following week and represented 51 per cent of the total creatinine ten days after treatment had been resumed. At that time the changes in cholesterol concentration and in the basal metabolic rate had not yet shown a tendency to return to their previous values.

In the case of the cretin (fig. 9) a few observations were made before thyroid treatment was begun. The patient had not received any treatment for six or eight months prior to her first visit to the hospital. At that time she excreted only 22 per cent creatine. After a few days of thyroid medication this rose to 35 per cent. Continued administration of thyroid for three months brought the level of urinary creatine to 60 per cent of the total creatinine. Immediately after discontinuance of thyroid the excretion of creatine diminished conspicuously, while that of creatinine decreased only slightly. Creatine fell to 42 per cent and then to 27 per cent of the total creatinine during the first week after discontinuance of thyroid, and it remained at 26 per cent during the second week. After treatment was resumed it rose, reaching 57 per cent on the tenth day. The changes in excretion of creatine are so similar

in the 2 cases that one can draw the conclusion that it is lack of the thyroid hormone alone which accounts for these fluctuations in creatinuria.

We had been puzzled by the low value for creatine and creatinine during the first days of observation of the child with thyroidectomy and by the sudden increase after thyroid was discontinued. This observation is in contrast to all experience with hypothyroidism. The few reported studies concerning creatine and creatinine excretion in thyroidectomized animals [38] cannot be used for comparison, since they were carried out on fully grown animals and furthermore do not agree.

In an attempt to repeat this unusual finding we discontinued thyroid medication for a second time, in January 1937. The child was under observation in the outpatient department; the mother collected a few twenty-four hour specimens at home after careful instruction. The child received her usual diet, including meat. Although the creatine tolerance

TABLE 2.—*Excretion of Creatinine and Creatine Under the Influence of Thyroid Medication and Its Withdrawal**

Date, 1937	Creatinine		Creatine, Mg.	Creatine Percentage of Total Creatinine	Thyroid, Mg.
	Total, Mg.	Preformed, Mg.			
Jan. 6	573	270	303	53	60
Jan. 10	392	230	162	41	None
Jan. 20	452	278	174	38	None
Jan. 29	696	282	414	59	30
Feb. 3	565	280	285	50	30
Feb. 17	664	296	368	55	45

* Thyroid discontinued from January 8 to 21.

of the hypothyroid child is higher than that of normal children, nevertheless a part of the food creatine reappears in the urine. In our patient the actual amount of creatine and its percentage in total creatinine were higher at this time than during the first observation, made when she was receiving a diet low in creatine. The drop in the excretion of creatine was marked, whereas the creatinine value remained almost stationary (table 2). The paradoxic changes noted previously, namely, that both the creatine and the creatinine value rose after thyroid medication was discontinued, could not be demonstrated again. We feel that the value obtained in the first period must have been altered by an error in the method, of which we were not aware at that time. This inconsistency

38. Frontali, G.: Sur le métabolisme de la créatine-créatinine dans le jeûne et après la thyroïdectomie totale, Arch. internat. de physiol. **13**:431, 1913. Schenk, P.: Der Einfluss der Schilddrüse auf den Kreatin-Kreatininstoffwechsel, Arch. f. exper. Path. u. Pharmakol. **95**:45, 1922. Takahashi, Y.: Der Einfluss der Schilddrüse und der Epithelkörperchen auf den Kreatinin- und Kreatinstoffwechsel, abstracted, Kongresszentralbl. f. d. ges. inn. Med. **45**:751, 1927.

does not affect the validity of the observation that the relation of urinary creatine and creatinine changes in the same direction, the ratio of creatine to creatinine rising when thyroid substance is administered and falling when it is withdrawn, with postoperative and congenital athyreosis.

SUMMARY

A case of carcinoma of the thyroid gland in a 4 year old girl is presented.

Associated anomalies in development, which include congenital dislocation of the hips, cerebral calcification, retinal lesions and spina bifida occulta, are described. No satisfactory relation between these various lesions could be determined.

Studies of basal metabolism, serum cholesterol and creatine excretion following thyroidectomy are recorded.

Twenty other cases of carcinoma of the thyroid in children under 15 years of age are cited.

The general impression is gained that carcinoma of the thyroid in children usually shows a low grade of malignancy and that accordingly the prognosis is more favorable than in adults.

News and Comment

UNIVERSITY NEWS

Dr. S. van Creveld has been appointed professor of pediatrics at the University of Amsterdam, to succeed Prof. Cornelia de Lange.

PERSONAL NEWS

Prof. Pautrier to Be Honored.—A committee of his colleagues, friends and students have recently agreed to award Prof. L. M. Pautrier a medal of honor on his twentieth anniversary as a teacher at Strasbourg, France. This medal, the striking of which has been entrusted to Maitre Pommier, will be presented to Pautrier at a special session of the Dermatologic Reunion of Strasbourg on May 14, 1939. Any contribution of 100 francs or more entitles the donor to a reproduction of the medal.

Prize Awarded to Dr. Leonard G. Parsons.—The fifth award of the Dawson Williams Memorial Prize, which is given in recognition of work done in connection with pediatrics, has been made to Leonard G. Parsons, professor of children's diseases at the University of Birmingham. It was presented to him at the Plymouth meeting of the British Medical Association on July 19. Professor Parsons delivered the Dawson Williams Memorial Lecture, describing his work on the nutritional problems of childhood.

DEATHS

Dr. Max T. Zarfl, of Vienna, Austria, died on March 22, 1938, at the age of 62 years. He was a well known pediatrician and had done excellent work in many lines.

CORRECTION

In the article by Dr. William C. Black, entitled "Acute Infectious Gingivostomatitis ('Vincent's Stomatitis')," in the July issue (Am. J. Dis. Child. **56**:126, 1938), the last paragraph of the summary on page 158 was inadvertently omitted. This paragraph reads:

> "There is no specific treatment. Parenterally administered sulfarsphenamine is ineffective and should not be employed. It is important to maintain an adequate fluid intake and to insist on rest in bed during the febrile period. The mouth should be kept as clean as possible. The diet should be soft and nonirritating. Caustic, tissue-destroying applications should not be used."

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

NUTRITIVE VALUE OF LACTALBUMIN VERSUS CASEIN. M. C. KIK, Proc. Soc. Exper. Biol. & Med. **37**:129 (Oct.) 1937.

In experiments on rats it was found that gain in body weight was greater in animals fed a diet containing 8 per cent lactalbumin than in those fed a diet containing 8 per cent casein. The same was true when these substances were fed at 12 per cent levels. The nitrogen storage, as determined by examining the carcass for nitrogen and determining the percentage of food nitrogen stored, thereby determining the biologic value of the food, was again greater for lactalbumin than for casein at both the 8 and the 12 per cent level. The results of the paired feeding experiments indicated that 1 Gm. of nitrogen from the lactalbumin ration was as effective in promoting the functions of maintenance and growth as an average of 1.33 Gm. of nitrogen from the casein ration.

HANSEN, Minneapolis.

DIETARY CALCIUM AND p_H OF THE LOWER INTESTINE. E. C. ROBERTSON, Proc. Soc. Exper. Biol. & Med. **37**:140 (Oct.) 1937.

Young rats fed diets low in calcium have in the large intestine a content with a p_H of about 6, whereas control animals fed the corresponding adequate diet have an intestinal content with a p_H of about 7. When the calcium intake is low, stasis occurs, and when stasis occurs the reaction of the bowel content becomes acid. Possibly the greater acidity is due to the biochemical activity of the more numerous bacteria in the mineral-deficient animals. The higher proportion of protein in the cecal material might favor bacterial growth.

HANSEN, Minneapolis.

THE HORMONAL BASIS FOR "WITCHES' MILK." W. R. LYONS, Proc. Soc. Exper. Biol. & Med. **37**:207 (Oct.) 1937.

The lactogenic principle was detected in the urine of 4 newborn babies. It is suggested that "witches' milk" is formed in the infantile breast after successive stimulation with estrogen and the lactogenic principle. HANSEN, Minneapolis.

INFLUENCE OF POTASSIUM ON BLOOD SUGAR AND TISSUE GLYCOGEN. H. SILVETTE and S. W. BRITTON, Proc. Soc. Exper. Biol. & Med. **37**:252 (Oct.) 1937.

On administration of potassium (40 mg. per hundred grams of body weight) to rats, the formation of liver and muscle glycogen was completely suppressed, while the blood sugar rose over 100 per cent. No visible toxic effects were noted in these animals, given 0.4 per cent potassium as potassium acetate. When half the stated quantity of potassium was given, no significant changes occurred.

HANSEN, Minneapolis.

DECREASE IN CHOLESTEROL ESTER IN THE SERUM IN CHOLEMIA, DUE TO ITS FIXATION BY THE DISEASED HEPATIC PARENCHYMA. H. BEUMER, Jahrb. f. Kinderh. **146**:1 (Dec.) 1935.

A decrease in cholesterol ester in the blood serum is found in mild and severe forms of cholemia. It is looked on as due to the fixation of cholesterol ester by the diseased hepatic parenchyma. The comparative values of serum cholesterol ester are given for atresia of the bile ducts, acute yellow atrophy and catarrhal jaundice.

LANDAU, Hannibal, Mo.

WAYS OF PROMOTING NATURAL FEEDING. F. WEISS and A. HOLZEL, Jahrb. f. Kinderh. **146**:98 (Jan.) 1936.

Despite the decrease in maternal nursing the mortality of infants has decreased. This is attributed to more hygienic surroundings, immunizations and other measures. It is felt that maternal nursing for at least a few months is highly desirable.

LANDAU, Hannibal, Mo.

DIASTATIC FERMENT IN THE BLOOD: ITS PHYSIOLOGY AND CLINICAL SIGNIFICANCE IN DISTURBANCES OF CARBOHYDRATE METABOLISM IN CHILDREN. A. LOESCHKE, Jahrb. f. Kinderh. **146**:133 (Feb.) 1936.

The optimal value of the blood diastase varies with the age of the person. The premature child shows a low value. There is a steady rise from the first year until the onset of puberty. Following this there is a fall. The upper limit of normal was found to be 363, with numerous values varying from this down to 20, depending on the age.

No regular parallelism between blood diastase and urinary diastase was demonstrable.

LANDAU, Hannibal, Mo.

GRUELS, FLOUR AND THEIR DECOMPOSITION PRODUCTS IN THE DIETS OF INFANTS. E. MÜLLER, Jahrb. f. Kinderh. **146**:197 (March) 1936.

There is considerable discussion in this article, which cannot be well abstracted.

LANDAU, Hannibal, Mo.

DIFFERENTIATION OF HUMAN AND ANIMAL MILK. F. MORI, Monatschr. f. Kinderh. **71**:183 (Oct.) 1937.

In 1930 Weltmann described a reaction of blood serum. He found that markedly diluted serum regained its ability to coagulate on being heated only after addition of certain electrolytes, such as calcium chloride. Mori makes use of this procedure to differentiate human and cow's milk. He sets up a series of tubes containing various dilutions of the milks and differentiates between the two milks by the tubes in which precipitation occurs.

GERSTLEY, Chicago.

EFFECT OF WATER ON BLOOD SUGAR. A. VISANI, Wien. Arch. f. inn. Med. **31**:113 (Sept.) 1937.

From fifteen to sixty minutes after ingestion of a liberal volume of water during fasting, the level of the blood sugar will sink considerably. This decline is real and is independent of the dilution of the blood. It may reach a figure of 21 per cent. The dilution of the blood will never exceed from 3 to 4 per cent. The drop coincides with the peak of diuresis. If urinary excretion is in any way inhibited, the level of the blood sugar will sink only slightly. The drop is independent of hepatic function, since it occurs even in the face of severe damage to the liver. It is observed when fluid is given parenterally, thus passing by the liver. It is also not dependent on intact renal function, for it occurs in the presence of renal disease. The mechanism of the decrease is still obscure.

SCHLUTZ, Chicago.

Vitamins; Avitaminoses

ACTIVATABILITY OF MILK AS AFFECTED BY FEEDING ERGOSTEROL TO COWS. R. F. LIGHT, L. T. WILSON and C. N. FREY, J. Nutrition **14**:453 (Nov.) 1937.

The authors proposed to determine whether the absorption of ergosterol could be demonstrated by biologic methods and also whether the presence of ergosterol in milk increased its activatability as regards prevention and cure of rickets.

They found that an added 0.42 mg. of ergosterol per quart of milk increased the activatability of the milk. In fact, this milk acquired twice the antirachitic potency that ordinary milk attains with a comparable exposure to ultraviolet rays.

Previous experiments had revealed that plant sterols are not absorbed by animals. The authors substantiated this finding when they found that ergosterol fed to cows did not increase the activatability of the milk when the milk was exposed to ultraviolet rays.

MUNNS, Winnetka, Ill.

ANTIRACHITIC EFFICIENCY OF IRRADIATED CHOLESTEROL. J. S. HOOD and I. RAVITCH, J. Pediat. **11**:521 (Oct.) 1937.

To test the efficiency of irradiated cholesterol in corn oil as a preventive of rickets in outpatients Hood and Ravitch conducted experimental studies on 177 nonrachitic infants varying in age, at the beginning of the observation, from 1 to 5 months, with the majority under 3½ months. The observation lasted for from five to seven months. Ninety-two of the infants were white; 85, colored. The infants were divided into three groups according to the dosages of irradiated cholesterol. The racial distribution in these groups was made as equal as possible. The dosage in the lowest group was between 350 and 500 international units; in the intermediate group, between 675 and 900 international units, and in the highest group, between 950 and 1,200 international units. In only 2 infants, a white and a colored one, did rickets develop. The rickets was extremely slight, and occurred in infants in the group in which the dosage was lowest. The roentgenograms of 27 infants showed slight deviations from the normal at the lower ends of the radius and ulna. It was doubtful whether these deviations denoted incipient rickets or were within the range of normal variation. If these deviations represented rickets, they represented degrees of the disease so slight as to be meaningless. In 19 children these changes disappeared under treatment, and in 8 they were still present at the end of the study. They occurred chiefly in the white babies; in the two groups with the higher dosages they were exclusively in the white babies and in the group with the lowest dosage they were more numerous in the white than in the colored infants.

Two studies were made to test the effectiveness of irradiated cholesterol in curing rickets. During the roentgenologic examinations which preceded the preventive work, 41 babies were found who showed either incipient rickets or deviations from the classic normal at the lower ends of the radius and ulna which could not be interpreted and were termed doubtful. These infants were divided into three groups and given irradiated cholesterol in the same dosages as were used in the study of prevention of rickets. The period of treatment and observation was also the same as in the study of prevention. Of these 41 infants, 17 exhibited slight or moderate rickets. In all but a single infant cure was effected by the time the study was completed, and in the excepted infant signs of regression of the disease were present in the roentgenograms at the close of the study. The roentgenograms of 24 children showed doubtful changes. In all but 4 of the instances of doubtful changes, these disappeared during the study and in 2 of the 4 evidence of regression of the signs could be seen in the last roentgenograms. In the second curative test 5 infants with severe rickets were treated. Within one month after the administration of either 675 or 865 international units well marked healing showed itself in the roentgenograms.

These results are compared with others recorded in the literature. They suggest that the efficiency of irradiated cholesterol in oil in the prophylaxis of rickets is excellent. The results appeared equal or superior to those obtained with other antirachitic substances in oil when these were administered at a dosage level of approximately 400 to 775 international units. Though the curative tests were too limited in number to permit conclusions of a comparative nature, the impression was gained that irradiated cholosterol is a powerful antirachitic substance, fully equal to cod liver oil or viosterol unit for unit and perhaps superior.

FROM THE AUTHORS' SUMMARY (RAUH, Cincinnati).

RICKETS IN PALESTINE. B. GRUENFELDER, M. Rec. **146**:176 (Aug. 18) 1937.

Children in Palestine, even when they show rickets, do not suffer from head sweating. Epiphysial swellings, which are so so evident in Europe and America, are exceedingly rare in children born in Palestine. Thoracic deformities are also rare. Gruenfelder discusses briefly the roentgen findings in rickets, also light as an important factor in prophylaxis. The incidence of rickets in Palestine is low: Of 950 sick children admitted to the hospital, only 11 showed rickets. And among the 6,204 children seen in the outpatient clinic, only 57 showed rickets or were suspected of having it.

WILLIAMSON, New Orleans.

VITAMIN A DEFICIENCY AMONG SCHOOL CHILDREN IN LONDON AND CAMBRIDGE. M. K. MAITRA and L. J. HARRIS, Lancet **2**:1009 (Oct. 30) 1937.

The technic used in this study of children for deficiency of vitamin A was based, with minor modifications, on that described by Jeans and Zentmire involving the measurement of dark adaptation (partial night blindness) by means of the Birch-Hirschfeld photometer. In vitamin A deficiency or partial deficiency there is some degree of "night blindness" after exposure to bright light, also a diminished degree of recovery in the dark.

Among 200 elementary school children examined in the east of London and in Cambridge, from 22 to 36 per cent were "definitely subnormal," whereas at a public school examined at the same time none of the boys were "definitely subnormal."

In those showing deficiency, treatment with vitamin A brought about definite improvement.

Vitamin A deficiency was more prevalent among young children than among adolescents. There was no important sex difference.

LANGMANN, New York.

ROLE OF VITAMINS (VITAMIN H.). V. BAPTISTA, Ann. de pediat., Sao Paulo **1**:77 (Nov.) 1937.

Baptista discusses the cutaneous manifestations of the lack of this vitamin, namely, seborrheic dermatitis, dermatitis erythematosa and erythrodermia.

SANFORD, Chicago.

ROENTGENOLOGIC CHANGES IN THE SCAPULA OF THE RACHITIC CHILD. H. KILIAN, Ztschr. f. Kinderh. **59**:1 (Aug. 2) 1937.

Kilian found that in cases of florid rickets 74 of 482 roentgenograms showed changes in the scapula: Sixty-seven showed incurvation of the lower portion; 6, breaks in continuity of structure (*Unbauzonen*), and 1, infraction. Cupping of the inferior angle was also observed in many cases. All changes are due presumably to muscular pull on weakened bone.

SIEMSEN, Chicago.

INDICATIONS FOR THE TREATMENT OF RICKETS WITH A SINGLE LARGE DOSE OF CALCIFEROL (VITAMIN D_2). H. BRAULKE, Ztschr. f. Kinderh. **59**:18 (Aug. 2) 1937.

That rickets and tetany may be cured by a single large dose of vitamin D was discovered accidentally by Harnapp in 1935. Others substantiated his finding and found the method of treatment harmless. Braulke used a single dose of 15 mg. (600,000 units) of vitamin D in treating rickets in 50 children. The results, as evidenced clinically, serologically and roentgenologically, were more prompt than with the old method. When rickets was accompanied by tetany, calcium therapy could be omitted, and sedation was necessary in only a single case. Although the old method is preferable for the treatment of ordinary rickets and in prophylaxis,

the single large dose has definite advantages. Indications for its use are: (1) manifest and latent tetany; (2) moderate and severe rickets with acute infections (especially with pneumonia and pertussis) or with chronic infections; (3) rachitis gravis (when complicated by marked skeletal changes), and (4) the likelihood that treatment at home will be unsatisfactory. SIEMSEN, Chicago.

ASCORBIC ACID CONTENT OF FRUITS AND VEGETABLES IN SEASON. J. MELKA and L. MELKOVA, Bratisl. lékar. listy **16**:82 (Feb.) 1936.

A short discussion of the physiology and chemistry of ascorbic acid is followed by a résumé of observations on the relation of a low level of ascorbic acid (vitamin C) in the blood to increased incidence of streptococcic infection, clouding of the lens and other conditions. The daily requirement of 10 mg. is supplied by 15 Gm. of green pepper, 16 Gm. of kohlrabi, 40 Gm. of tomato, 77 Gm. of radish, 50 Gm. of turnip, 22 Gm. of lemon juice, 25 Gm. of orange juice, 220 Gm. of prune juice, and 330 Gm. of banana. STULIK, Chicago.

Hygiene; Growth and Nutrition; Public Health

DEVELOPMENT OF FAMILY CARE IN NEW YORK STATE. HIRAM G. HUBBEL, Am. J. Psychiat. **94**:551 (Nov.) 1937.

In addition to offering a financial saving to the state, care in a boarding home of mentally defective persons of certain types offers undoubted educational advantages over the accepted institutional care of such patients. Children and adults, wards of the Newark State School of New Jersey, are placed under supervisory care in foster homes in small communities or on farms. Association with normal persons helps many mildly defective patients toward satisfactory social and economic adjustment. With suitable training many of the children do creditable school work and make surprisingly good grades. Most of them may be taught by means of adapted occupation to become self-supporting. JAHR, Omaha.

FACIAL GROWTH IN RELATION TO DENTAL OCCLUSION. M. S. GOLDSTEIN and F. L. STANTON, Internat. J. Orthodontia **23**:859 (Sept.) 1937.

Charts and graphs are numerous in this article, which deals with the results of anthropometric measurements of the face and head and observations on dental occlusions. The subjects were groups of Jewish males, 50 in each group, the first group representing the age period from 2½ to 3½ years and the other groups representing every other year of life thereafter to and including 20½ to 21½ years. A group of old men averaging 74 years in age was also examined for effects of senility. LEWIS, Dayton. [ANGLE ORTHODONTIST.]

HYGIENE OF THE MOUTH. S. WOLFF, Bull. Assoc. internat. de pédiat. prevent. **4**:16, 1937.

Wolff stresses the need of more consideration, from a prophylactic point of view, of the tonsils and the teeth in childhood. Observations on the vital importance of these structures are of daily experience, not only in relation to local involvement but to digestive disorders and to even more remote complications.

Clear indications should be determined; the relative advisability of tonsillotomy, tonsillectomy or suction of the crypts is still a problem; the author favors the former operation. There is a conflict of opinion between physicians and dentists as to the treatment of diseases of the teeth, but all agree that anomalies of the palate, of the gums and of dentition should be appraised and cared for at the earliest possible moment. AMESSE, Denver.

FUNCTIONING OF THE INFANT WELFARE CENTER AT GISORS. L. DARDEL, Bull. Soc. de pédiat. de Paris **35**:313 (May) 1937.

This report concerns a rural infant welfare station. All the milk used had lime water added to it in the proportion of 25 Gm. to the liter. It was heated rapidly and then rapidly cooled. The milk obtained in this region was very rich, and it is believed that this accounted for the production of diarrhea in a number of infants, as the condition cleared up when weaker dilutions were used. The good effect of the work done was reflected in the infant mortality rate of the district, which was diminished by two-thirds. BENJAMIN, Montreal, Canada.

CHILD LABOR. LUIS B. PRIETO F., Bol. Inst. internac. am. de protec. a la infancia **11**:36 (July) 1937.

Among the conclusions in this article on child labor in Venezuela, the following statements are the most constructive: 1. Special treatment and care are necessary during the prepuberty period, when physiologic and psychologic disturbances are produced; child labor is dangerous at that time; therefore, it is necessary to raise, the age limit for children in industrial labor to 16 years at least. 2. In order to protect children and to prevent their being prematurely subjected to hard work it is indispensable to create committees of child protection to provide healthy recreation and collect the necessary funds to establish vacation colonies for working minors in all communities. LESLIE, Evanston, Ill.

REPORT ON THE CHILD WELFARE WORK ACCOMPLISHED BY THE CHILDREN'S COUNCIL, URUGUAY. RODOLFO QUESDADA PACHECO, Bol. Inst. internac. am. de protec. a la infancia **11**:261 (Oct.) 1937.

The author, who is a medical inspector of regional homes and hospitals in the Argentine Republic, gives a report on his visit to several institutions of the Children's Council (Uruguay). FROM THE EDITOR'S SUMMARY.

THE SOCIAL TREATMENT OF THE NEGLECTED CHILD. ROBERTO BERRO, Bol. Inst. internat. am. de protec. a la infancia **11**:305 (Oct.) 1937.

The author indicates the greater complexity of the problem of neglect in adolescence and the necessity of studying and solving each case as a separate problem. FROM THE EDITOR'S SUMMARY.

IN DEFENSE OF AN INSTITUTE OF RHEUMATOLOGY AND CARDIOLOGY AT THE FACULTY OF MEDICINE IN BUENOS AIRES. MAMERTO ACUSA, J. de pediat., Rio de Janeiro **4**:415 (Oct.) 1937.

An interesting discussion of the necessity of such an institution is presented in this paper. SANFORD, Chicago.

EXAMINATION OF INFANTS IN MUKDEN IN 1936. I. SAITO, J. Orient. Med. **27**:795 (Nov.) 1937.

Of the 484 healthy infants examined in Mukden, China, in 1936, only 16.3 per cent were found to measure up to the normal standard in all respects. The body weight of mothers whose infants were superior in weight was found to be higher than that of mothers of infants below the standard measurements. The weight of the fathers showed no constant relationship to that of the offspring. Consanguinity of the parents was present in 5.4 per cent of all cases, and breast feeding was practiced in 85.6 per cent. Pallor was noted in 35.4 per cent, and in 50 per cent the development of subcutaneous fat and muscle was poor. The margin of the liver was palpable in 87.4 per cent, and in 20 per cent the spleen was also

palpable. In children over 10 months of age the spleen was not felt. Beading of the ribs occurred in 34.9 per cent, Harrison's grooves in 22.3 per cent and craniotabes in 14 per cent. In many of the infants who displayed signs of infantile rickets teething was delayed.

KATO, Chicago.

INFANT MORTALITY IN NORTH SWEDEN. U. HJÄRNE, Hygiea **99**:609 (Sept. 15); 667 (Sept. 30) 1937.

Hjärne studied the mortality rate of infants in two northern districts of Sweden. He found that whereas the average mortality rate of infants in Sweden in 1934 was only 47.4 per thousand, in the years from 1928 to 1933 in north Sweden, the rate was 73.7 per thousand. In some of the southern districts and in the two largest cities in the years from 1931 to 1935 the rate was 40 per thousand; in Göteborg in 1935, it was only 27 per thousand. Hjärne discusses the probable causes of this increase in mortality among infants of north Sweden and concludes that the only obvious reason for it is the mothers' unsatisfactory knowledge of the care and feeding of their children and the lack of competent control. He advocates the introduction of infant welfare centers.

WALLGREN, Göteborg, Sweden.

Prematurity and Congenital Deformities

ARACHNODACTYLY. JULIEN HUBER, J.-A. LIÈVRE and HECTOR, Bull. Soc. de pédiat. de Paris **35**:49 (Jan.) 1937.

A tall, thin boy aged 12 years, whose father was of similar build, is described. He had long slender extremities, an asymmetric pigeon breast and flat feet. There was no abnormality of the lens or iris of either eye, but myopia was present.

BENJAMIN, Montreal, Canada.

MULTIPLE MALFORMATIONS IN A CHILD: FUSION OF CERVICAL VERTEBRAE, CERVICAL RIBS, ELEVATION OF THE SCAPULA AND APLASIA OF THE OPPOSING MUSCLES OF THE RIGHT THUMB. M. LANCE, Bull. Soc. de pédiat. de Paris **35**:124 (Feb.) 1937.

A boy aged 6 years had fused posterior arches of the third and fourth cervical vertebrae; six cervical spinous processes, although seven vertebral bodies were present; a complete seventh cervical rib on the right and an incomplete seventh cervical rib on the left; aplasia and elevation of the right scapula; and aplasia of the right thenar eminence, causing absence of opposing movement of the thumb.

BENJAMIN, Montreal, Canada.

ARACHNODACTYLY: REPORT OF A CASE. C. ROEDERER, Bull. Soc. de pédiat. de Paris **35**:225 (April) 1937.

A boy aged 14 years was extremely tall and had long extremities. He had scoliosis and kyphosis and a funnel-shaped chest. The head was dolichocephalic. Photographs of the boy are reproduced.

BENJAMIN, Montreal, Canada.

ARACHNODACTYLIA. J. MALBRÁN and H. R. PÍCOLI, Arch. de oftal. de Buenos Aires **12**:3 (Jan.) 1937.

After a detailed review of the literature on the symptomatology of arachnodactylia and the influence of heredity since this disease was first described by Marfan in 1896 as "dolichostenomelia" and a full discussion of the different theories concerning etiology, the authors report a series of cases in 2 families.

In the first family a father and 3 children were affected. (Two other children were not examined but were reported to have sound eyes.) The father did not

have any osseous lesions, and ocular examination revealed atrophy of the iris, subluxation of the lens, detachment of the retina and atrophy of the optic nerve in one eye and subluxation of the lens in the other eye. The mother was healthy. A boy aged 14 had irregular development of the feet and also cardiac lesions (pulmonary sclerosis). The right eye showed subluxation of the lens upward and choroidal lesions, and the left eye, subluxation of the lens. A girl aged 10 years had flat feet, elongated toes and fingers and aortitis. There was subluxation of the lens in each eye. A girl aged 6 years had dolichocephalic hands, arachnodactylia, lordosis, aortic sclerosis and dilatation of the heart. Examination of her eyes showed miosis and luxation of the lens upward; the fundi were normal.

In the second family the mother and 3 daughters (of 7) were examined. The mother had syphilitic iritis, was tall and presented lordosis, marked development of the hands and feet (her father was also large) and elongation of the fingers and toes, which were not deformed. Examination of her eyes showed deposits of pigment on the posterior surface of the cornea and the anterior lens capsule and no luxation of the lens. Of the 3 daughters, only 1 showed signs of the disease. She was aged 12 years, was retarded in development and had Hutchinson teeth, a broad nose, rhagades and a high palate. She was above normal in stature; the long bones were markedly developed, and the hands showed indications of arachnodactylia. She had lordosis and flat feet. The right eye showed microphthalmia, with microcornea and luxation of the lens upward. The lens was opaque, with broad synechia at the inferior pole, vascular penetration and no vision. The left eye showed microphthalmia and microcornea. The cornea was transparent, the lens normal and the vitreous clear. Doyne's choroiditis was present at the posterior pole of the eye, and there were peripheral pigmentary changes. Vision with correction of the refractive error (myopia) was 1.

C. E. FINLAY. [ARCH. OPHTH.]

THE ELECTROCARDIOGRAMS OF PREMATURE INFANTS. M. R. BAILA and D. AGUILAR GIRALDES, Rev. méd. latino-am. **22**:755 (April) 1937.

The electrocardiograms of premature infants studied did not differ from those of full term infants.

DWYER, Kansas City, Mo.

ACHONDROPLASIA: REPORT OF A CASE. MARCOS STEINSLEGER, Rev. Soc. de pediat. de Rosario **2**:147 (Sept.) 1937.

The author reports a case in which achondroplasia occurred in a 3 month old child. Roentgenograms accompany the article.

SANFORD, Chicago.

THE PATHOLOGIC PICTURE OF BILATERAL CONGENITAL ANOMALIES OF THE VERTEBRAL BODIES: THE NORMAL DEVELOPMENT OF THESE BONES. K. HARTMANN, Fortschr. a. d. Geb. d. Röntgenstrahlen **55**:531 (June) 1937.

This paper presents a monographic treatment of the subject matter expressed in the title. It is copiously illustrated and contains a comprehensive bibliography.

McCUNE, New York.

HYPERPHALAGIA OF THE MIDDLE FINGER WITH BILATERAL PARTIAL BRACHYDACTYLY (AFFECTING THE FIRST, SECOND AND THIRD FINGERS). H. LOSSEN, Fortschr. a. d. Geb. d. Röntgenstrahlen **56**:428 (Sept.) 1937.

This uncommon, familial and hereditary anomaly was first described by Geelvink more than thirty years ago. Eleven instances have been reported in the medical literature up to the present time; to this number Lossen adds another illustrative case. It is urged that further cases be reported in order to clarify the pathogenesis of the anomaly.

McCUNE, New York.

CONGENITAL DEXTROCARDIA WITH COMPLETE TRANSPOSITION OF VISCERA. C. Y. D. TYAU, Chinese M. J. **52**:439 (Sept.) 1937.

A case is reported of a young woman who had no disturbance of health in childhood to suggest a congenital physical abnormality. The development of tuberculosis furnished the occasion for a physical examination, and situs inversus was discovered.

NEFF, Kansas City, Mo.

GARGOYLISM. A. TEN BOKKEL HUININK, Maandschr. v. kindergeneesk. **6**:448 (Aug.) 1937.

The author gives a description of a typical case of gargoylism, the patient being a girl aged 5 years. The diagnosis was formed because of the following symptoms: mental retardation; massive structure of the head; depression of the base of the nose; abnormal distance between the eyes; prominent abdomen with hypertrophy of the liver and the spleen; opaque corneas, and typical deformities of the skeleton.

VAN CREVELD, Amsterdam, Netherlands.

ACARDIUS ACORMUS. J. H. BRENNINKMEYER, Nederl. tijdschr. v. geneesk. **81**:4256 (Sept. 4) 1937.

The author presents a description of a case of acardius acormus, in this special case better called pseudocormus (Barkow). The monster was one of twins; the first, of apparently normal development, died after five days (vitium cordis?). The other, apparently only a head, showed parts of the vertebral column and anterior ribs in the roentgenogram. A recess at the base of the head contained a heart, its pulsations lasting an hour and a half after birth; its short umbilical cord took its origin from the umbilical cord of the normal partner.

VAN CREVELD, Amsterdam, Netherlands.

THE HEREDITY OF ALBINISM. J. SANDERS, Nederl. tijdschr. v. geneesk. **81**:4932 (Oct. 16) 1937.

One hundred and forty families with 216 albino members are described. The author concludes that the heredity of albinism is monorecessive. He emphasizes the data on 2 families in which both dominant albinismus circumscriptus and recessive albinismus totalis are present. He is of the opinion that these heterozygotes are an exception to most heterozygotes, who nearly always are phenotypically normal.

VAN CREVELD, Amsterdam, Netherlands.

OPERATIVE MANAGEMENT OF CLEFT PALATE. P. R. MICHAËL, Beitr. z. klin. Chir. **161**:468, 1935.

A great deal of work, together with accumulated statistics, bears out the fact that it is not possible to reach a definite conclusion as to what should be done in every case of cleft palate. The author usually operates in two sittings and finds that he gets better anatomic and functional results because of this. He emphasizes the importance of preoperative management of the mouth and teeth.

RUBIN, Boston.

MANAGEMENT OF HARELIP. K. LUHMANN, Beitr. z. klin. Chir. **161**:539, 1935.

Luhmann describes his technic for the surgical management of harelip.

RUBIN, Boston.

Newborn

THE RISK TO THE INFANT IN BREECH DELIVERY. THOMAS R. GOETHALS, Surg., Gynec. & Obst. **62**:525 (March) 1936.

In a clinical study Goethals analyzes the risk of primary breech presentation to 1,242 infants born in this manner during a twenty-two year period. The gross

mortality was 25.7 per cent, which was over twice the mortality rate for general deliveries at the Boston Lying-In Hospital during a ten year period. Breech deliveries occurred in 3.97 per cent of all births, 30,655 being observed in a twenty-two year period. Analysis of the figures showed that infants delivered by breech were premature three times more frequently than newly born infants in general. The pathologic conditions of pregnancy had an important effect in producing the high gross mortality rate, as the incidence of placenta praevia, ablatio placentae and prolapse of the cord was three, five, and five times as frequent with breech presentation as with all other types of delivery. Excluding macerated fetuses and grossly malformed babies, uncomplicated breech delivery of 916 infants resulted in a mortality of 13.6 per cent; this figure was subdivided into 53.6 per cent for the premature, 10 per cent for the immature, and 6.9 per cent for the mature infants. In Goethals' final summing up it is indicated that a mortality rate of 6.9 per cent represents the risk to living undeformed full term infants delivered by breech.

LAW, Ann Arbor, Mich.

PEMPHIGUS NEONATORUM. A. K. BOWMAN, Brit. J. Dermat. **48**:484 (Oct.) 1936.

The author describes his method for treating pemphigus neonatorum. The skin is gently swabbed with ether, and the bullae, with a surrounding area of about 1 inch (2.5 cm.) in radius, are painted with a 3 per cent solution of mercurochrome. The patient is then immersed in a bath of 8 per cent solution of boric acid, and the blister is removed by the firm but circumscribed movement of a sterile cotton-tipped applicator—a fresh applicator for each blister. The opening of all the lesions having been completed, the child is removed from the bath and swathed in an absorbent towel. A second painting of each infected spot with mercurochrome follows. The painted areas are then allowed to dry by evaporation, and the whole of each stained area is covered with one or two layers of collodion.

With this method some 40 patients were successfully treated, and it is claimed for this form of treatment that it is a "specific measure reduced to its simplest terms."

RATTNER, Chicago. [ARCH. DERMAT. & SYPH.]

CONGENITAL ICHTHYOSIS WITH RECOVERY. ÉCALLE and SUZOR, Bull. Soc. d'obst. et de gynéc. **26**:717 (Nov.) 1937.

The infant described weighed 2,900 Gm. at birth. The skin had a varnished appearance, as though collodion had been applied to the entire body, covering it with a membrane through which the color of the underlying skin could be seen. This was bright red at birth but gradually took on the color of light brown ocher. The skin was dry on palpation and devoid of all elasticity. There was ectropion of the lids, and the conjunctivas were congested. The eyeballs could not be seen. There were fissures in the collodion-like layer of the skin, particularly in the region of the flexures. These gradually increased in number until by the tenth day of life they were well distributed over the entire body. With the confluence of the fissures there occurred a shedding of the outer layer of the skin, suggestive of the casting off of the skin which occurs in certain animals. The skin gradually took on a normal appearance except for scattered infected areas. The lids returned to normal, and the general condition of the infant was satisfactory. Histologic examination of a section of the skin showed thickening of the corneal layer, with no change in the true skin. The child appeared normal at about the age of 3 weeks. The author states that in this case some developmental abnormality must have interfered with the normal desquamation of the corneum into the amniotic fluid before birth, so that the child was born with the membrane described. A photograph of the child is presented with the text.

GLASER, Rochester, N. Y.

MONGOLISM IN THE NEWBORN. PÉHU and BROCHIER, Bull. Soc. d'obst. et de gynéc. **26**:720 (Nov.) 1937.

The authors report that in 1937, among 1,000 births, they observed 7 cases of mongolism. They state that the condition is rarely recognized during the first three days of life, although the characteristic signs, which they discuss at length, are already present. The authors also review the various theories as to the cause of the condition. They point out that external causes of nervousness probably do not play a part. During the war, when Paris and London were subjected to aerial bombardment, there was no increase in the number of persons with mongolism. They state that the most consistent cerebral lesions associated with the condition are hypoplasia of the diencephalon, especially the mamillary bodies, the hypophysis and infundibulum, the tuber cinereum and the subthalamic areas. The authors recommend prolonged treatment of the condition with large doses of pituitary, thyroid, adrenal and gonad extracts. At the age of 3 to 4 years special education is indicated. A good result is, however, rarely attained.

GLASER, Rochester, N. Y.

OBSTETRIC PARALYSIS OF THE INFERIOR EXTREMITIES. M. LANCE, Bull. Soc. de pédiat. de Paris **35**:25 (Jan.) 1937.

A girl, aged 2½ years when seen by the author, was born by frank breech extraction. The lower extremities were swollen and immobile after birth. The paralysis persisted, and there were incontinence of urine and marked constipation, apparently associated with difficulty in defecation. The whole syndrome was considered to be due to involvement of the cauda equina.

BENJAMIN, Montreal, Canada.

PECULIAR CRANIAL DEFORMITY IN A NEWBORN INFANT. BRAULIO XAVIER FILHO, Pediat. e puericultura **6**:47 (March) 1937.

The deformity reported by the author seems to have been a combination of oxycephaly and exencephaly. Photographs are shown. SANFORD, Chicago.

ICTERUS GRAVIS: CURE BY REPEATED BLOOD TRANSFUSIONS. F. DE BOER, Maandschr. v. kindergeneesk. **7**:24 (Oct.) 1937.

A woman aged 28, who had borne first 2 normal children and then 6 children with hydrops universalis all of whom died, gave birth to a child with moderate edema, an enlarged liver and a palpable spleen. At daylight the child appeared to have icterus gravis neonatorum; examination revealed 17 per cent of erythroblasts in the blood and a strongly positive bilirubin reaction of the urine. The child's life was saved by means of repeated blood transfusions, of which the first was given immediately after birth. VAN CREVELD, Amsterdam, Netherlands.

Acute Contagious Diseases

POLIOMYELITIS (POLIOMYELOPATHIA) CHRONICA: REPORT OF A CASE, WITH A HISTOLOGIC STUDY. A. T. STEEGMANN, Arch. Neurol. & Psychiat. **38**:537 (Sept.) 1937.

Steegmann reported a case of chronic poliomyelitis in one who had had a previous attack of acute poliomyelitis. From histologic study, he concluded that the case was one of progressive spinal muscular atrophy and that the term "chronic poliomyelitis" is a misnomer. He offered a suggestion that the previous attack of acute poliomyelitis may have been a predisposing factor in the disease.

BEVERLY, Chicago.

COMMUNICABLE DISEASE CONTROL IN PRIVATE PRACTICE. C. A. STEWART and E. S. PLATOU, J. A. M. A. **109**:1520 (Nov. 6) 1937.

Stewart and Platou discuss the optimal time for immunization in reference to various communicable diseases. They suggest that inoculation against smallpox and against pertussis be performed before the age of 6 months and inoculation against diphtheria, against scarlet fever and against typhoid fever during the next twelve months or more. Their experiences with immunizations against pertussis and scarlet fever are presented, including those in a few instances of lack of protection.

Emphasis is laid on the discovery of tuberculosis in the child, on careful observation for the development of complicating types of this disease later and on the extension of the work to trace the source of foci of tuberculosis, particularly within the household group, as a means of eradicating this communicable disease.

HEERSMA, Kalamazoo, Mich.

DURATION OF IMMUNITY AGAINST DIPHTHERIA ACHIEVED BY VARIOUS METHODS. W. H. PARK, J. A. M. A. **109**:1681 (Nov. 20) 1937.

Park reviews the literature and compares, as regards their efficiency in immunizing against diphtheria, fluid toxoid, alum-precipitated toxoid and toxin-antitoxin. He finds that many of the experiments were improperly controlled as to the initial and final Schick tests and as to the determinations of antitoxin, the dosages, the number of injections of the immunizing agents, the age of the patient, the number of interval Schick tests, the lengths of interval before the final tests, and the number of persons tested. His only suggestions are that perhaps two or three doses of toxoid rather than one dose should be given and that a combination of alum-precipitated toxoid with fluid toxoid, the one following the other, may be of even more value.

HEERSMA, Kalamazoo, Mich.

IMMUNITY TO SMALLPOX. M. V. HUBBARD and D. T. LOY, J. A. M. A. **109**:1997 (Nov. 27) 1937.

Hubbard and Loy report their experiences in the vaccination of 1,000 entrants to a Kansas college against smallpox. The reactions were read as immune, or immediate, in 38.5 per cent; primary take in 19.6 per cent; secondary take, occurring in students with a vaccination scar or a history of smallpox, 7 per cent; accelerated, or early, in 35 per cent. The results indicate that 61.5 per cent were in some degree susceptible to smallpox and that 26.5 per cent had no protection against the disease. Although these figures are higher than those for urban areas, the authors recommend vaccination of all college entrants.

HEERSMA, Kalamazoo, Mich.

PURIFICATION AND CONCENTRATION OF DIPHTHERIA TOXIN: III. SEPARATION OF TOXIN FROM BACTERIAL PROTEIN. M. D. EATON, J. Bact. **34**:139 (Aug.) 1937.

Eaton describes methods for separating toxin and bacterial protein by isoelectric point fractionation. Measurements of the amount of bacterial protein in purified toxin were based on titrations, by means of the precipitin test, of the antibacterial serum against preparations containing known amounts of bacterial protein. The results indicate that the bacterial protein constitutes from 0.5 to 2 per cent of the total protein in the most highly purified preparations. Slightly denatured toxin is precipitated at a higher p_H and a lower concentration of ammonium sulfate and is more readily adsorbed on magnesium or aluminum hydroxide than is undenatured toxin. Evidence is presented that the porphyrins found in crude and purified toxins are not combined with protein but are precipitated near the isoelectric point of toxin and are easily adsorbed on protein precipitates. The purified protein, which has been freed from all but small traces of impurities detectable by the methods employed, is diphtheria toxin.

STOESSER, Minneapolis.

A Study of Meningococci Recovered in the United States Since 1930. S. E. Branham and S. A. Carlin, J. Bact. **34**:275 (Sept.) 1937.

An extensive study of this subject has been made by the authors. In their study 409 strains of meningococci from the spinal fluid and blood of persons with meningococcic infection and 42 strains from carriers, received since 1930, have been typed according to the classification first presented by Gordon and Murray, in 1915. Of the strains from patients with active infection, 352 (86 per cent) fell into the I-III group (including types I and III and strains agglutinated equally well by both serums); 48 (11.7 per cent) were of type II. Of 42 strains from carriers, 24 (57 per cent) were of type II, and 12 (or 28.5 per cent) were of group I-III. Of these 12 I-III strains, 8 were from persons who were in immediate contact with patients whose infections were due to that type of meningococcus. Apparently type II has been relatively unimportant as a cause of epidemic meningitis in the United States during the last decade. On the other hand, the prevalence of type II among the carriers studied, and the relatively greater occurrence of this type in cases of active infection during the endemic years of 1932 to 1935 throws some light on the possible significance of this group. The authors conclude by stating that it is impossible to judge at this time whether the epidemiologic differences noted between groups I-III and II occur as a rule or are an accident of this decade.

Stoesser, Minneapolis.

Intranasal Administration of a Pertussis Antigen. S. S. Schooten, J. Michigan M. Soc. **36**:849 (Nov.) 1937.

Schooten reports on a soluble antigen prepared from Haemophilus pertussis which he used in the treatment of 20 patients in the period from November 1936 to April 1937.

Nine patients had been ill one week, 7 two weeks and 4 over fifteen days, before treatment began.

Ten drops of the antigen were placed in each nostril daily from four to nine times (average, six).

Marked improvement was observed in 10 (50 per cent) of the patients; definite improvement, in 8, and none in 2.

The author believes the results sufficiently encouraging to warrant further trial of this antigen by others.

Carey, Detroit.

Influence of Vitamin C Deficiency on the Resistance of Guinea Pigs to Diphtheria Toxin; Glucose Tolerance. A. Sigal and C. G. King, J. Pharmacol. & Exper. Therap. **61**:1 (Sept.) 1937.

Dextrose tolerance was used to determine the influence of vitamin C on the resistance of guinea pigs to diphtheria toxin. In animals receiving just enough vitamin C to prevent scurvy toxin in sublethal doses decreased dextrose tolerance to a greater extent than it did in animals with a higher intake of vitamin C.

Pilcher, Cleveland.

Does Digitalis Protect Against Diphtheria Toxin? C. W. Edmunds and R. G. Smith, J. Pharmacol. & Exper. Therap. **61**:37 (Sept.) 1937.

Some years ago the senior author had shown that digitalis was useless in diphtheria intoxication in animals. More recently some one in another laboratory reported that digitalis administered to guinea pigs poisoned with diphtheria toxin was to a considerable degree life saving.

The present paper reports that digitalis, ouabain and strophanthin showed protective action against the injurious effects of diphtheria toxin on guinea pigs. This report confirms the earlier one and is in agreement with that of Gold and Klump

on their observations in cats. It is worth while recalling that the senior author also demonstrated the great value of 10 per cent dextrose solution injected by vein in poisoning with diphtheria toxin.

PILCHER, Cleveland.

THE FLEA IN TYPHUS FEVER. B. J. BAROODY, M. Rec. **146**:333 (Oct. 20) 1937.

The fact is that a flea may transmit typhus fever as well as a body louse. The fleas which harbor the infectious virus, Pulex irritans, are found on sewer rats. These rats have and die from typhus fever. The flea carrying the virus will leave the rat, using the dog as a host, though the dog is not susceptible. The flea may inoculate man, through its defecations rather than its bite.

WESTON JR., Columbia, S. C.

HUMAN CONVALESCENT SERUM IN THE TREATMENT OF SCARLET FEVER. J. C. FOX and D. FISHER, Mil. Surgeon **81**:356 (Nov.) 1937.

A cooperative plan for the distribution of convalescent serum has been successfully developed between the Sixth Corps Area and the Samuel Deutsch Serum Center. Objective and subjective improvement followed the use of adequate serum (40 cc.). There was also a definite lowering of the incidence of complications. No untoward reactions were observed.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **52**:1693 (Nov. 26) 1937.

For the period from Oct. 10 to Nov. 6, 1937, the incidence of poliomyelitis dropped to 879 cases. This was lower than in 1935 and 1936 but higher than in 1932 and 1934. In all sections the incidence appears to have been on the increase during the past fall, with the South Atlantic region least affected. During the same period 7,200 cases of measles were reported. This is the largest number for this period in the last nine years. The incidence of meningococcic meningitis and that of influenza were slightly above normal, and the incidence of smallpox, 487 cases, was nearly double normal. The incidence of diphtheria, of scarlet fever and of typhoid was below normal. The mortality from all causes was 10.9 per thousand, which is about average.

SANFORD, Chicago.

REFLECTIONS ON POLIOMYELITIS. J. SAUCIER, Union méd. du Canada **66**:1011 (Oct.) 1937.

In looking back on the recent epidemic of poliomyelitis in Ontario, Saucier stresses present ignorance of the important points of the disease. The portal of entry is not certainly known. Passive immunization is deceptive and perhaps actually dangerous; active immunization is definitely dangerous. Adult blood seems to carry some protection. Nasal applications of alum and zinc sulfate have not completely protected experimental animals.

Saucier concludes, "A few children contract poliomyelitis. A very few have residual paralysis. Infinitely few die."

DAFFINEE, Boston.

LARYNGEAL DIPHTHERIA AND TRACHEOTOMY. W. NAPIER, Lancet **2**:673 (Sept. 18) 1937.

During an eleven year period (from 1926 to 1936) there were in the City of Glasgow Fever Hospital 2,528 cases of diphtheria, of which 220, or 8.7 per cent, were laryngeal cases. Of these 220 cases, tracheotomy was performed in 55, with a case mortality rate of 6.8 and an operation death rate of 25.5 per cent. Early operation is advocated. Pneumonia, toxemia and unrelieved obstruction contributed alike to the mortality.

The routine treatment for the child with croup not in need of immediate operation consisted of use of the steam tent, application of poultices to the neck and chest and administration of stimulants when necessary. Serum, given intramuscularly, was used with moderation (from 8,000 to 12,000 units), since large doses may aggravate obstruction by causing too rapid separation of the membrane.

As to tracheotomy, in place of the maxim "In hospital, interfere late," Napier would substitute "In hospital, interfere as early as possible in the case in which the disease is advancing."

LANGMANN, New York.

CLINICAL AND EXPERIMENTAL STUDIES ON MALIGNANT DIPHTHERIA. A. STROE and D. HORTOPAN, Arch. de méd. d. enf. **40**:681 (Nov.) 1937.

The wave of diphtheria which has swept over Europe during the past decade has permitted clinicians to make intensive investigations of many obscure features in this disease. Therapeutic problems particularly have occupied the attention of many observers, in their endeavor to lower the rising mortality rates, which in some areas reached the disquieting figure of 50 per cent. Tables are published comparing the death rates in diphtheria for the principal countries of Europe between the years 1924 and 1934, together with charts of similar statistics for Bucarest, Rumania. In the latter city there was a definite increase in the number of patients with malignant diphtheria: from 7 per cent of the total number in 1927 to 12 per cent in 1934. The authors report on a series of cases, numbering 102, all of the malignant form. The frequency of grave manifestations is noted; among these are extension of the false membrane, cervical adenopathy with edema, cardiovascular complications, hemorrhagic involvement, renal disturbances and early paralyses. Next infection, especially with streptococci and anaerobes, seemed uncommonly frequent in this series.

In the treatment of grave conditions, very large doses of antidiphtheritic serum, from 40,000 to 100,000 units, were employed, and if the response was not satisfactory this dose was repeated on the second and on the third day. In view of the frequent association of diphtheria with anaerobic infections, antigangrenous serum was combined with diphtheria antitoxin. The results were excellent, comparing favorably with those obtained in malignant scarlet fever through a combination of mixed serotherapy.

AMESSE, Denver.

TREATMENT OF SEVERE ATTACKS OF DIPHTHERIA WITH LARGE DOSES OF STRYCHNINE. G. PAISSEAU and P. CARREZ, Arch. de méd. d. enf. **40**:710 (Nov.) 1937.

Since their first contribution on the use of strychnine in the treatment of diphtheria was published in 1935, Paisseau and Carrez have had further experience in the use of this drug as an adjuvant to specific therapy.

It was brought out by Jannette-Walen that normal tolerance to strychnine is much higher than is commonly believed and that in diphtheria, especially, this tolerance is greatly augmented. It appears to increase during the period of late childhood, and in intoxications such as that following massive doses of the barbiturates one may freely administer enormous doses of strychnine. The use of a heavy dosage is facilitated by the fact that this drug is rapidly eliminated from the body; there is no cumulative effect. The only contraindication of strychnotherapy in diphtheria is croup, in which the tendency to spasm would be increased. Nephritis seems to support intensive treatment.

These observers use a solution of 0.2 per cent for subcutaneous injection, and from 2 to 3 mg. is given every twenty-four hours in ordinarily severe diphtheria, while in the malignant form 1 mg. per kilogram is offered daily as a minimum. If conditions warrant heroic measures, daily doses up to 3 mg. per kilogram may be exhibited without marked danger. It is stressed throughout the discussion, however, that treatment with strychnine must be considered only as a complement to serotherapy, which in all cases covered by this report was given according to accepted methods.

AMESSE, Denver.

ELECTROCARDIOGRAPHIC INVESTIGATION OF THE OCULAR CARDIAC REFLEX IN THE DIPHTHERITIC AND IN THE NONDIPHTHERITIC PATIENT: ITS DIAGNOSTIC VALUE IN DEMONSTRATING MYOCARDITIS IN DIPHTHERIA. G. BORGIOTTI, Riv. di clin. pediat. **35**:886 (Oct.) 1937.

Electrocardiographic studies were made on 6 patients with diphtheria; 3 of them had severe postdiphtheritic paralysis, 2 moderate postdiphtheritic paralysis and 1 no paralysis. None of the patients showed any clinical or electrocardiographic signs of myocarditis. On ocular compression the electrocardiogram revealed vagal slowing and also definite disappearance of the auricular P wave and appearance of a ventricular rhythm with normal R and T waves. In the controls the vagal slowing was of longer duration than in the diphtheritic patients; otherwise, no electrocardiographic abnormalities were present. These studies are believed to have shown cardiac alterations which would not have been picked up by other means and which therefore have a diagnostic and prognostic value.

HIGGINS, Boston.

TREATMENT OF ERYSIPELAS. C. DE AZEVEDO and A. GRUMSER, Arch. de pediat., Rio de Janeiro **10**:65 (Nov.) 1937.

Despite the apparently beneficial results reported from vaccine therapy and treatment with sulfanilamide, the authors believe that the most favorable results can be obtained with ultraviolet rays from the mercury vapor lamp.

SANFORD, Chicago.

NONPARALYTIC FORMS OF POLIOMYELITIS. E. A. BERETERVIDE, J. de pediat., Rio de Janeiro **4**:494 (Nov.) 1937.

Poliomyelitis may be divided into three types: (1) the abortive, (2) the paralytic and (3) the nonparalytic, which may in turn be divided into a meningeal form and a form involving the central nervous system. In the latter the reflexes are hyperactive rather than paralyzed. These classes are discussed.

SANFORD, Chicago.

PREVENTIVE IMMUNIZATION AGAINST SCARLET FEVER WITH PRECIPITATED TOXIN. F. FARAGÓ, Orvosi hetil. **81**:857 (Aug. 21) 1937.

For preventive immunization against scarlet fever, use was made of a toxin (exotoxin) precipitated with aluminum hydroxide and purified. The standard toxin of the National Institute of Health, Washington, D. C., was used. Three injections were given; the whole dose was between 20,000 and 29,000 skin test doses. The children immunized numbered 4,355. In from four to twelve weeks, between 90 and 96 per cent of these immunized children gave negative reactions when submitted to the Dick test. In five villages the preventive immunizations stopped the epidemic, whereas in the control villages the epidemic lasted longer. Reactions were seldom observed: from 47 to 63 per cent of the inoculated children did not show any reactions; in from 27 to 53 per cent there were some local reactions and only in 0.5 per cent did a scarlatiniform eruption appear.

GÖTTCHE, Budapest, Hungary.

IMPROVEMENT OF PROPHYLACTIC INHALANTS AGAINST SCARLET FEVER. G. ISHIYAMA, J. Orient. Med. **27**:381 (Aug.) 1937.

Ishiyama studied four types of antigen: (1) a normal vaccine (0.0084 cc. of hemolytic streptococci in 1 cc. of physiologic solution of sodium chloride, heated at 60 C. for thirty minutes); (2) a concocted suspension (heated at 100 C. for thirty minutes); (3) a clear medium (clear supernatant fluid obtained by centrifugation of the concoction), and (4) a substituted suspension (obtained by sub-

stituting physiologic solution of sodium chloride for the clear medium of the concoction). The following results were obtained: 1. With the normal vaccine the collateral effect and the formation of agglutinins in the blood and in the lung extract were most marked. 2. In regard to the formation of agglutinins in the blood and in the lung extract, the concocted suspension had a greater effect than the clear medium or the substituted suspension, but the secondary effects were entirely absent. Ishiyama therefore believes that the concocted suspension of scarlatinal hemolytic streptococci is the most desirable prophylactic inhalant against scarlet fever.

KATO, Chicago.

GERMAN MEASLES WITH MENINGOENCEPHALITIS. E. ADLER, Hygiea **99**:774 (Oct. 31) 1937.

This is a description of rubella encephalitis in 2 girls 16 and 12 years old. In the former the nervous symptoms (headache and vomiting) began eight days after the eruption. She was first seen a fortnight later. She had no fever. The expression was masklike, there was urinary retention, and ataxia and the Babinski sign were noted on both sides. There was no stiffness of the neck and no Kernig sign. A lumbar puncture was performed. The spinal fluid was limpid, showed an increase in globulin and 21 cells per cubic millimeter, almost exclusively mononuclears. This patient was discharged improved after one month. At reexamination a fortnight later she was found healthy. In the second girl the encephalitic symptoms set in six days after the eruption, with fever, headache and vomiting. She was first seen two days later because of convulsions. She was then delirious and hyperesthetic, with stiffness of the neck. The spinal fluid was limpid and showed an increase in globulin and 61 mononuclear cells per cubic millimeter. Recovery was rapid and the patient was discharged healthy after two weeks.

WALLGREN, Göteborg, Sweden.

THE NEED OF HOSPITAL TREATMENT OF CHILDREN WITH PERTUSSIS. R. BERGMAN, Svenska läk.-sällsk. förhandl., Sept. 30, 1937, p. 245.

In Sweden during the last decade more children died from whooping cough than from scarlet fever, diphtheria and typhoid fever together. A decrease of the mortality from pertussis can be expected if certain groups of children with this disease can be given hospital care. In many cases the disease in itself is of such a malignant type that treatment in a hospital is necessary; in others the social condition in the family is so unsatisfactory that it is impossible to guarantee appropriate care of the sick child; in a third group of cases contamination of uninfected infants and small children cannot be prevented without removal of the coughing child to a hospital. In the years from 1933 to 1935, 238 children with whooping cough were admitted to the Hospital for Contagious Diseases in Stockholm. Of these, 8 died (3.4 per cent). For the first year of age, the figures were 53 cases and 3 deaths (5.2 per cent).

WALLGREN, Göteborg, Sweden.

Acute Infectious Diseases

GONORRHEAL SEPSIS IN AN INFANT. S. G. HOFFMAN and M. SCHNEIDER, J. A. M. A. **109**:1447 (Oct. 30) 1937.

Sepsis occurring as the result of gonorrheal ophthalmia is nearly unheard of. An infant aged 4 days was admitted to the hospital with gonorrheal ophthalmia. Twelve days later the temperature became elevated and the wrists became swollen. Later new swellings appeared in the knees. Cultures of the blood revealed gonococci. The clinical diagnosis was confirmed at autopsy.

BONAR, Salt Lake City.

RHEUMATIC FEVER AS A FAMILIAL DISEASE: ENVIRONMENT, COMMUNICABILITY AND HEREDITY IN THEIR RELATION TO THE OBSERVED FAMILIAL INCIDENCE OF THE DISEASE. MAY G. WILSON and MORTON D. SCHWEITZER, J. Clin. Investigation **16**:555 (July) 1937.

This paper presents a consideration of environment, contagion and heredity as factors responsible for the familial incidence of rheumatic fever in 112 families observed over periods ranging from three to eighteen years. The studies indicate that a hereditary factor making the bearer susceptible to rheumatic fever was transmitted as a single autosomal recessive gene. The exact role of environment and contagion in the acquisition of the disease by susceptible persons could not be determined.

GUEST, Cincinnati.

ATTEMPTS TO TRANSMIT FOWL PARALYSIS. CARL OLSON, J. Infect. Dis. **61**:325 (Nov.-Dec.) 1937.

"Attempts were made to transmit fowl paralysis to normal chickens by means of intraneural implantation of affected nerve tissue, and by means of a cross circulation of the blood between a diseased and a normal chicken. The experiments were met with uniform failure."

TOOMEY, Cleveland

A NEW SIGN IN THE DIAGNOSIS OF ACTIVE RHEUMATIC DISEASE IN CHILDHOOD. CHARLES J. BRIM, M. Rec. **146**:119 (Aug. 4) 1937.

The author gives a detailed description of nodules which appear on the anterior faucial pillars of the throat and which extend to the contiguous structures. These nodules constitute a definite objective physical sign and are seen in a large number of children who suffer from active rheumatic infection. There may be other manifestations of the disease present, or the presence of the nodules may be the only sign preceding the appearance of later manifestations. The prevalence of the nodules is dependent on the activity of the rheumatic infection, and their value as a sign lies in their diagnostic and prognostic significance.

WILLIAMSON, New Orleans.

ACTION OF P-AMINO BENZENE SULPHONAMIDE [SULFANILAMIDE] AGAINST STREPTOCOCCAL INFECTIONS IN MICE. S. P. DE and U. P. BASU, Indian J. M. Research **25**:465 (Oct.) 1937.

Streptococci from patients with erysipelas and puerperal sepsis were injected into mice. The minimum lethal dose was determined. Sulfanilamide (paraaminobenzenesulfonamide) protected the mice from these two infections.

SNELLING, Toronto, Canada.

TYPHOID PERITONITIS BY EXTENSION. JULIEN HUBER, CAYLA and VELCIU, Bull. Soc. de pédiat. de Paris **35**:91 (Feb.) 1937.

A girl aged 8 had typhoid with peritonitis and ascites. Owing to her poor condition, operation was not performed. At autopsy no evidence of perforation of the bowel could be found. The lymph glands within the abdomen were enlarged, but none showed softening or rupture. The terminal part of the ileum showed mononuclear infiltration which extended through Peyer's patches, and there was vascular congestion, with obliteration of many small vessels in the mucosa by thrombi. Apparently organisms passed through into the peritoneum.

BENJAMIN, Montreal, Canada.

STAPHYLOCOCCIC SEPTICEMIA IN AN INFANT TREATED SUCCESSFULLY BY CONTINUOUS INTRAVENOUS PERFUSION. P. LEREBOULLET, R. JOSEPH and J. BRINCOURT, Bull. Soc. de pédiat. de Paris **35**:117 (Feb.) 1937.

A girl aged 3 months had a staphylococcic empyema on the right side, which was drained surgically. Two months later the upper extremity of the left humerus

showed an area of osteomyelitis, which cleared up spontaneously. Staphylococcus aureus was recovered from the urine. The baby's condition became progressively worse, and a fatal termination seemed imminent. A continuous intravenous drip was begun and was used for four days. Recovery ensued. The infant weighed 3.4 Kg.; from 5 to 6 liters of 5 per cent dextrose in saline solution was injected into the vein.

BENJAMIN, Montreal, Canada.

RHEUMATISM. A. G. GOLDENBERG, Rev. franç. de pediat. **13**:305, 1937.

This review on the subject of rheumatism serves to show how confused and unsatisfactory is the present knowledge of the etiology, pathogenesis and treatment of this all too prevalent condition.

LESLIE, Evanston, Ill.

OBSERVATIONS ON MYOCARDITIS IN GRIP. J. KRAMÀR, Riv. di clin. pediat. **35**:936 (Oct.) 1937.

In Hungary a number of children have recently been observed to have myocarditis during infections of the upper part of the respiratory tract or during the course of influenza; rheumatic fever was ruled out as the cause.

HIGGINS, Boston.

INTESTINAL PARASITES IN CHILDHOOD. ELIEZER AUDIFACE, J. de pediat., Rio de Janeiro **4**:392 (Sept.) 1937.

A short discussion on intestinal parasites in childhood is presented.

SANFORD, Chicago.

THE COURSE OF TYPHOID IN IMMUNIZED SUBJECTS. I. F. DONTCHENKO, Vrach. delo **19**:479, 1937.

Dontchenko reports his observations on the course of typhoid in 619 patients, divided for the purposes of study into two groups. The first group comprised 263 patients who had previously received specific immunization, while the second comprised 356 nonimmunized persons.

The author's observations revealed that the course of the disease in immunized patients was much less severe than in the nonimmunized and that the frequency of all complications as well as the mortality rate was definitely lower in the same. The frequency of the total complications, which included myocarditis, pneumonia, intestinal perforation and peritonitis, was equal to 12.6 per cent in the immunized group and 24 per cent in the nonimmunized group, while the mortality rate was 3.8 per cent in the former and 9.8 per cent in the latter.

The author's observations are in favor of the specific immunization against typhoid.

BODER, Los Angeles.

CURE OF A TYPHOID CARRIER BY CHOLECYSTECTOMY. E. A. C. BUYZE, Nederl. tijdschr. v. geneesk. **81**:5536 (Nov. 13) 1937.

The author presents the case of a typhoid carrier 8 years old who infected her father. The father infected 5 other members of the family, 4 of whom died. The carrier was cured by cholecystectomy.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

DEMONSTRATION OF THE TUBERCLE BACILLUS IN THE PULMONARY TUBERCULOSIS OF CHILDHOOD. S. CAMPBELL, Arch. Dis. Childhood **12**:321 (Oct.) 1937.

Of 50 children who were suspected of having pulmonary tuberculosis, 12 showed the tubercle bacillus in the sputum, feces or stomach washings. In 9 of the 12 cases

in which the tubercle bacillus had been isolated, sputum was obtained, and in 5 of these cases it yielded the tubercle bacillus. Feces were examined in a number of the cases, but in no case was the bacillus found in the feces when it could not be demonstrated in one of the other materials. In 7 instances the tubercle bacillus was found in direct smears of the stomach washings. In 10 of the 12 cases in which the tubercle bacillus was found in the sputum, feces or stomach washings, the stomach washings were inoculated in guinea pigs and cultured, and the tubercle bacillus was isolated from the guinea pigs in 5 of the instances and in the cultures in 8. Owing to the possibility of epidemics among guinea pigs, attention is drawn to the danger of relying entirely on inoculation of these animals as a method of diagnosis. Whatever the lesion, the tubercle bacillus is found most frequently in children under 3, and this in spite of the greater difficulty of examining patients in this period of life.

KELLY, Milwaukee.

ONSET OF TUBERCULOSIS FOLLOWING TONSILLECTOMY. E. W. PHILLIPS, Dis. of Chest **3**:8 (Oct.) 1937.

Investigation among 829 tuberculous patients in a sanatorium revealed that 22 per cent had undergone tonsillectomy. More than one third of these were in the third decade of life, and one half of the latter had been operated on to relieve general constitutional symptoms attributed to focal infection and had the onset of their pulmonary tuberculosis within two years after the operation. This was true to a somewhat lesser extent among the adolescent patients, while the patients operated on in childhood in this series had tuberculosis develop, on the average, twelve years after tonsillectomy.

Phillips urges that before tonsillectomy is performed, patients, particularly adults and adolescents, be investigated more carefully by physical examination and study of roentgenograms—whether their complaints are local or constitutional.

HEERSMA, Kalamazoo, Mich.

PATHOLOGIC CHANGES IN THE EAR IN LATE CONGENITAL SYPHILIS. O. MAYER and J. S. FRASER, J. Laryng. & Otol. **51**:683 (Nov.) 1936.

The extreme rarity of histologic examination in cases of deafness due to late congenital syphilis induced Mayer and Fraser to combine their anatomic material. They think that their investigation of the histologic and pathologic changes in the ear will render the clinical symptoms more readily understandable. The peculiarity of the ear trouble of congenital syphilis, apart from its connection with keratitis parenchymatosa and dental deformities, lies in the fact that it usually appears in apparently healthy persons, generally females, between the tenth and the twentieth year and that, once started, the deafness progresses rapidly, becoming pronounced overnight in some cases. Usually there is no pain, but the patient complains of tinnitus and frequently of giddiness. The tympanic membrane is perfectly normal or may be slightly infiltrated. The deafness is labyrinthine, but occasionally the middle ear may be slightly affected. Functional examination of the labyrinth frequently shows peculiar and inexplicable combinations of reactions. Although many cases have been studied clinically, the number in which there were anatomic and histologic examinations is small. The authors review the 5 cases that have been reported in the literature and then describe their own observations. They report first 3 cases in which late congenital syphilis was demonstrated clinically or anatomically and then 2 cases in which the diagnosis was made histologically only.

The first case is histologically interesting because of the extensive chronic gummatous osteomyelitis which cannot be ascribed to chronic suppurative otitis media or to tuberculosis but must be considered syphilitic. In the second case also the changes in the ear were characteristic of syphilis. According to the history in the third case, there can be no doubt that the condition was typical of congenital syphilis. Labyrinthine changes were the cause of the deafness. In the fourth case the middle ear was normal. The changes detected in the inner ear

had been considered signs of meningococcic inflammations of the labyrinth, because the middle ear could not be looked on as the starting point of the trouble. This view was disproved by the condition of the semicircular canals and the bone of the labyrinthine capsule. The semicircular canals exhibited a most peculiar active chronic periostitis, characterized by being subperiosteal. Apart from this periostitis, the authors observed extensive chronic osteomyelitis of the labyrinthine capsule, with occasional nodules of lymphocytes, epithelioid cells and giant cells. Since cancellous bone was also formed, there was some resemblance to otosclerosis, but there were no "foci" in this case, the new bone being extremely irregular, as it usually is in inflammatory processes. The perivascular inflammatory infiltration, which was obvious everywhere, differentiated the condition at once from otosclerosis. Cerebral hemorrhage, which was the cause of death, points to syphilis, and so do the articular changes. The case must be considered as one of late congenital syphilis. The gummatous inflammation at a limited portion of the anterior meatal wall is worthy of special mention as having induced the cholesteatoma in the external meatus. In the fifth case the diagnosis was osteomalacia, but the histologic picture of the ear undoubtedly points to late syphilis and probably to late congenital syphilis.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

VACCINATION WITH BCG. A. WALLGREN, Ann. de méd. **42**:407 (Oct.) 1937.

This is a survey of the present state of BCG vaccination. The importance of employing the vaccine in such a manner that the children become tuberculin sensitive and are protected against virulent infection during the period of incubation of the vaccine is emphasized. From a theoretic point of view, the vaccination cannot be of any prophylactic value against secondary and tertiary tuberculous disease but may, if it has any immunizing effect, prevent the more severe forms of primary tuberculosis. A restricted number of reported reliable follow-up studies on vaccinated children speak in favor of such an effect of the vaccination.

WALLGREN, Göteborg, Sweden.

CUTANEOUS SENSITIZATION TO TUBERCULIN OBTAINED WITH HISTAMINE. J. HUBER, J. A. LIÈVRE and J. J. WELTI, Bull. Soc. de pédiat. de Paris **35**:150 (Feb.) 1937.

Following a report that the cutaneous reaction to tuberculin could be made more sensitive by using a mixture of equal parts of tuberculin and a 1:10,000 solution of histamine hydrochloride, a boy 12½ years old whose cutaneous reaction to tuberculin had been negative was tested with old tuberculin in an area in which 0.25 mg. of histamine had been injected intradermally. The reaction thus obtained was more marked than that with tuberculin alone, although on a second trial the test with tuberculin was also positive.

BENJAMIN, Montreal, Canada.

CONCERNING HISTAMINE ASSOCIATED WITH TUBERCULIN SKIN REACTIONS. P. P. LÉVY and P. CHASSAGNE, Bull. Soc. de pédiat. de Paris **35**:156 (March) 1937.

Twenty-two children were given skin tests with tuberculin. For half of the children a drop of the tuberculin was united with a drop of a 1:1,000 dilution of histamine and for the other half a drop of tuberculin was placed on an area of skin into which histamine was injected intradermally and the area scarified. In the former group 5 children who had given positive reactions to tuberculin showed two negative results, one faintly positive result and two positive results, when the tuberculin was mixed with histamine; in the second group the results in the unmodified tests and in those performed after injection of histamine were identical. It is recommended that tests performed with tuberculin in association with histamine should be controlled by unmodified tests until more definite knowledge is obtained regarding the effect of histamine on the test.

BENJAMIN, Montreal, Canada.

TUBERCULOUS LESION OF THE FACE IN A CHILD. H. JANET, MME. ODIER-DOLLFUS and E. WOLINETZ, Bull. Soc. de pédiat. de Paris **35**:232 (April) 1937.

A girl 2 years old had an ulcerative lesion at the root of the nose and a submaxillary abscess. Smears from the base of the ulcer as well as from pus drained from the abscess showed acid-fast bacilli. Cultures from similar material were sterile. The tuberculin test was positive. In the absence of evidence that the tuberculin test was negative previous to the appearance of the lesion on the face, one cannot be certain that this was a primary tuberculous infection of the skin, but the authors presume that it was.

BENJAMIN, Montreal, Canada.

THE ROENTGENOLOGIC PICTURE OF PULMONARY TUBERCULOSIS IN CHILDHOOD. A. PIERGROSSI, Radiol. med. **24**:811 (Oct.) 1937.

Piergrossi divides pulmonary infiltrative tuberculosis into two groups, the epituberculous infiltration and the evolutive form. The former is found mostly in infants and is associated with a tuberculous focus with hyperergic reactivity about it. Of this form one can distinguish the primary and the secondary types. The evolutive form has also a central focus and progresses with the formation of cavities. This is due to feeble resistance on the part of the patient, together with increased reactivity of the organisms. Evolutive pulmonary tuberculosis is caused by progression from a primary focus. The secondary form is lobar and is characterized by an active onset and a circumscribed progressive ulcerous process.

FROM AUTHOR'S SUMMARY.

AN UNUSUAL CASE OF TUBERCULOSIS IN EARLY INFANCY. G. FROLA, Lattante **8**:559 (Oct.) 1937.

A girl of 17 months died of miliary tuberculosis, and a necropsy was performed. The tuberculous infection was probably air borne and had localized in the brain, caseous nodules being found in the right cerebrum, cerebellum and parietal bone. A breakdown of one of these foci resulted in the development of miliary tuberculosis of the lungs and tuberculosis of the intestine.

HIGGINS, Boston.

PULMONARY TUBERCULOSIS IN INFANTS. C. DE RITIS, Lattante **8**:581 (Oct.) 1937.

De Ritis reports 6 fatal cases of pulmonary tuberculosis in infants of from 2 to 10 months of age. The symptoms were insufficient, and the roentgenograms not convincing enough, for a diagnosis of tuberculosis. However, the diagnosis was clinched by the finding of tubercle bacilli in the pharyngeal secretions of each patient.

HIGGINS, Boston.

SYPHILITIC HEPATITIS WITH ASCITES IN TWO INFANTS. M. RADICI, Riv. di clin. pediat. **35**:812 (Sept.) 1937.

In these infants, 28 days and 6 months old, respectively, hepatitis was due neither to miliary gummas nor to focal gummas but to diffuse intralobar proliferation of the connective tissue, with atrophy of the hepatic parenchyma.

HIGGINS, Boston.

TUBERCULOUS PERITONITIS IN AN INFANT. C. PELFORT, Arch. de pediat. d. Uruguay **8**:577 (Sept.) 1937.

Pelfort reports this condition in an infant 21 months old. The most prominent symptom was marked ascitis. This disappeared after two abdominal paracenteses. Three months later symptoms of miliary tuberculosis developed, which resulted fatally. At autopsy, in addition to the miliary process, plastic adhesive tuberculous peritonitis was found.

SCHLUTZ, Chicago.

Differentiation of Active and Prophylactic Stages of Childhood Tuberculosis. J. Riha, Bratisl. lékar. listy (supp.) **16**:1 (Jan.) 1936.

Riha discusses at length the controversial points in definition, prophylaxis, infection, reinfection, occult tuberculosis, dissemination and diagnosis of activity. He stresses the difficulty of diagnosing primary pulmonary infection and especially of extrapulmonary foci because of the scarcity of symptoms and because the presence of antibodies in the blood serum is still undeterminable.

Stulik, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

Hyperplasia and Regeneration of the Myocardium in Children. H. E. MacMahon, Am. J. Path. **13**:845, 1937.

Evidence is presented in the form of mitotic division of the nuclei of heart muscle fibers to indicate, first, that in cardiac hypertrophy in infants proliferation of heart muscle fibers can take place, and second, that in severe myocardial injury in children regeneration of myocardial elements can occur.

From the Author's Summary. [Arch. Path.]

Mental Changes Including Aphasia in a Patient with Sickle Cell Anemia. Beulah Bosselman and S. H. Kraines, Am. J. Psychiat. **94**:708 (Nov.) 1937.

A Negro boy aged 13 with sickle cell anemia of six years' duration suddenly showed mental changes, including aphasia. The aphasia, in the authors' opinion, is explainable on the basis of small multiple cerebral hemorrhages.

Jahr, Omaha.

Congenital Displacement of the Tricuspid Valve (Ebstein's Disease): Review and Report of a Case with Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System. Wallace M. Yater and Morse J. Shapiro, Ann. Int. Med. **11**:1043 (Dec.) 1937.

The authors record the sixteenth instance of this anomaly. The patient was a woman aged 21. Results of electrocardiographic studies and of a histologic examination of the conduction system by means of 4,500 serial sections accompany the report.

Reading, Galveston, Texas.

The Incidence of Heart Disease in Cases of Sydenham Chorea. Paul L. Parrish, Leo M. Taran and Saul Starr, J. Pediat. **11**:617 (Nov.) 1937.

This paper presents the results of a study of the incidence of cardiac disease in a group of children who had had one or more attacks of Sydenham chorea uncomplicated by any rheumatic manifestation and a comparison of this incidence with the incidence of cardiac disease in a group of children presenting histories of chorea plus other manifestations of rheumatism. Seventy-eight of the children had histories of one or more attacks of chorea without any rheumatic manifestations, and 34 children had had both chorea and rheumatic symptoms. Of the entire group, 59.8 per cent had definite cardiac involvement. The incidence of cardiac involvement in the "pure chorea" group was 52.5 per cent and in the mixed group 76.4 per cent. These statistics are at variance with those of Jones and Bland, who found only a 3 per cent incidence of cardiac involvement in patients with "pure chorea." From their studies it would seem that chorea and rheumatic fever are separate and distinct entities. The authors' figures agree with the older observations of Frazier and Koplik and have led them to conclude that until the causes of rheumatism and chorea are known it is reasonable to assume that chorea is one of the rheumatic manifestations.

Rauh, Cincinnati.

NIEMANN-PICK'S DISEASE. F. R. B. ATKINSON, Brit. J. Child. Dis. **34**:245 (Oct.-Dec.) 1937.

This article consists of a résumé of 42 cases of Niemann-Pick's disease reported in the literature, with supplementary comments by the author. He points out that although the disease is always called a familial disease it is uncommon for more than one member of a family to be affected. The disease is rapidly fatal, and nearly all the children in the 42 cases died within the second year after birth.

Hypercholesteremia is common, and neutral fats show a marked increase. Epstein states that when Niemann-Pick's disease is present the amount of lecithin and cephalin is more than one hundred times normal, and the amount of sphingomyelin, about one hundred and ten times normal.

It is now generally held that Niemann-Pick's disease is due to a disordered metabolism of the lipoids.

The relation of Niemann-Pick's disease and Tay-Sachs' disease is still a matter of dispute.

LANGMANN, New York.

SPLENIC ANEMIA IN AN INFANT OF FIFTEEN MONTHS (VON JAKSCH-LUZET SYNDROME): SPLENECTOMY. A. ARONDEL, R. BUREAU and DRAUNET, Bull. Soc. de pédiat. de Paris **35**:333 (June) 1937.

A boy aged 15 months had pallor and splenomegaly. The blood showed anemia, leukocytosis and many nucleated red cells. The bleeding time was seventeen minutes, and there were hemorrhage and purpura. As no improvement followed the usual antianemic treatment, splenectomy was performed. There was no recurrence of hemorrhage after this, but anemia persisted for some time and then abruptly began to improve. Histologically, the spleen showed sclerosis of the follicles and pulp, myeloid transformation and macrophagic reaction. The child died of pneumococcic meningitis seven months after the splenectomy.

BENJAMIN, Montreal, Canada.

SCHULLER-CHRISTIAN'S DISEASE: REPORT OF A CASE. BOISSERIE-LACROIX, SERVANTIE, P. DUPUY and LAVIAL, Bull. Soc. de pédiat. de Paris **35**:351 (June) 1937.

A boy aged 8 was dwarfed and had marked exophthalmos. He had signs of increased intracranial pressure. At first a tentative diagnosis of meningioma of the lesser wings of the sphenoid bone was made. Roentgenographic examination of the skull revealed numerous defects in the vault, some of which seemed to perforate the bone. The sella turcica was somewhat enlarged and rounded, and the surrounding bone was striated. The sutures were spread, especially the frontoparietal suture. The orbital arches were normal, but there were intraorbital masses, that on the right being larger than that on the left. The mandible was moth-eaten in appearance and showed two defective areas. The anterior part of the left ilium was defective. There was no diabetes insipidus. The teeth were not loose. There was some eczema. The tongue showed marginal glossitis. The liver and spleen were normal. Biopsy of material taken from the skull yielded soft, friable yellowish material which showed cholesterol crystals surrounded by lipoid reticuloendothelial cells and some giant cells. The cytoplasm stained orange with sudan III. A biopsy of the cutaneous tissue showed no xanthomatous cells. One of the lacunas of the skull became infected, and pus obtained from it showed streptococci. Many chemical determinations were made, most of which showed normal values. Radiotherapy was followed by some diminution of intracranial pressure, but the exophthalmos became worse and the bony defects increased slightly. Thyroid extract was also administered.

BENJAMIN, Montreal, Canada.

THE FRAGILITY OF THE RED CELLS IN THE FIRST MONTHS OF LIFE. F. AUXILIA, Riv. di clin. pediat. **35**:1066 (Dec.) 1937.

Forty-six observations were made on the fragility of the red blood cells of 23 infants during the first few days of life; the method of Simmel was used. The

tendency was for the red blood cells to be hemolyzed more readily by hypotonic salt solutions than were the red blood cells of older children. Observations on infants as jaundice developed showed no marked increase in the fragility of the erythrocytes; thus jaundice did not explain the increased fragility of the red blood cells of the newborn.

HIGGINS, Boston.

HEMOCYTOBLASTIC LEUKEMIA. LUIS PRUSS and TOMAS OCANA, Rev. Soc. de pediat. de Rosario **2**:125 (Sept.) 1937.

Examination of the blood of a 10 year old child showed from 50,000 to 78,000 leukocytes per hundred cubic centimeters of blood. Seventy-eight per cent of the leukocytes were hemocytoblasts.

SANFORD, Chicago.

CALCIFICATION OF THE PERICARDIUM. O. RUMMERT, Fortschr. a. d. Geb. d. Röntgenstrahlen **55**:241 (March) 1937.

This paper provides a comprehensive review of the literature and a copious bibliography relating to calcification of the pericardium. Although calcification is seldom detected before adult life, the fundamental causes in many cases appear to originate in childhood.

MCCUNE, New York.

EROSION OF THE RIBS IN A CASE OF CONGENITAL COARCTATION OF THE AORTA. K.-H. KROHN, Röntgenpraxis **9**:776 (Nov.) 1937.

This paper calls attention to the well known notching of the inferior margins of the ribs, which is likely to be present in cases of congenital stenosis of the aorta. An illustrative case is presented, together with diagrams intended to clarify the pathogenesis of the lesion.

MCCUNE, New York.

HISTOLOGIC CHANGES IN THE BLOOD-FORMING ORGANISMS OF THE GROWING BODY WITH DIFFERENT DIETS. W. P. PLONSKY, Pediatria, 1937, p. 19.

A diet rich in protein influences to a large degree the hemopoietic organs. A carbohydrate diet is second in influence. A diet rich in fat leads to a depression of the hemopoietic system. With a diet rich in lipoid materials the polymorphonuclears increase in number and the lymphocytes diminish. Under the influence of a carbohydrate diet the monocytes increase. A diet rich in protein causes an increase in lymphocytes.

MCKHANN, Boston.

A SIMPLE METHOD OF STUDYING THE RETRACTION OF THE BLOOD CLOT. A. ALMQUIST, Acta pædiat. **20**:115, 1937.

The shrinkage or retraction of the clot which forms during coagulation of whole blood is generally regarded to be a function of the numerical and physiologic integrity of the thrombocytes; failure of, or prolonged delay in, clot retraction is one of the characteristic hematologic findings in cases of thrombocytopenic purpura. The older methods of demonstrating the phenomenon have the disadvantage that they require at least 1 cc. of blood; this imposes the necessity of venipuncture. None of the micromethods are entirely satisfactory.

At Wallgren's clinic in Göteborg, Sweden, the following procedure has been worked out: The blood is drawn by pricking the skin and is collected into U-shaped capillary tubes about 1 mm. in diameter, the limbs of which are between 4 and 5 cm. long. The specimen is at once placed in a damp chamber to prevent evaporation. By virtue of the fact that during the preliminary period of retraction the clot remains more or less firmly attached to the walls of the tube at each end, longitudinal contraction causes it to occupy an elevated position in the transverse member of the U-tube; this phenomenon makes it easier to demonstrate the begin-

ning of retraction. After a time the clot pulls away from its attachment in the limb which was not used in filling the tube. After this it shrinks rapidly until a consistent minimum length is reached.

Two hundred such tests were performed with the blood of 80 persons, some sick, some well, but all having normal platelet concentration, and with the blood of 6 patients with thrombocytopenia. That of members of the first group showed incipient retraction within ten to fifteen minutes; retraction was clearcut within from one to two hours. Failure of retraction in the presence of a normal platelet count could always be traced to technical error in performing the test. In 2 cases of Werlhof's disease retraction was completely absent. In the 4 cases of thrombocytopenia due to leukemia the results were somewhat variable. Generally speaking, there was a satisfactory correlation between the concentration of platelets and the occurrence and time of onset of clot retraction.

McCUNE, New York.

Diseases of Nose, Throat and Ear

TONSILLECTOMY FOR TONSILLAR ABSCESS. A. LINCK, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **141**:255, 1936.

According to Linck, it is now generally recognized that in the treatment of paratonsillar abscesses tonsillectomy is helpful and necessary. That tonsillectomy during the acute stage does not involve the dangers formerly ascribed to it is likewise no longer questioned. However, about the time and the general or selected application of tonsillectomy opinion is still divided. The majority of clinicians and practitioners still advise incision during the acute stage and recommend tonsillectomy only as a secondary operation. Tonsillectomy without previous incision is considered justified only in cases in which there are complications or especially severe involvement. The author, however, is of the opinion that abscess tonsillectomy, with complete exclusion of incision, should be performed as the primary intervention in all cases in which a paratonsillar abscess either is clinically demonstrable or appears probable. He regards incision in addition to tonsillectomy, within the complete therapeutic program, as entirely superfluous and often harmful. Moreover, he does not think that a comparison is justified between incision and abscess tonsillectomy, for incision is only a partial treatment, with limited therapeutic aims and possibilities, whereas abscess tonsillectomy represents a complete treatment, with the aim of complete and final arrest of the process. The author estimates the two treatments from three different standpoints: the risk involved in the abscess, the results of the two operations and the risk involved in the two operations. He reaches the conclusion that there is only one factor that could be cited against the general performance of abscess tonsillectomy, namely, the conviction that the tonsils are indispensable to the patient and that they should be preserved even in cases of paratonsillar abscess. This, however, contradicts the accepted opinion, which he regards as definitely established.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

ACUTE OTITIS MEDIA WITH SUBLABYRINTHINE EMPYEMA. H. RICHTER, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **142**:28, 1936.

Richter observed that the pneumatic cells, which in many persons are underneath the labyrinth, that is, between the labyrinth and the tympanic floor on the one side and between the bulb of the jugular vein and the posterior cranial fossa on the other, often are not given sufficient attention. Careful attention to these sublabyrinthine cells is important, not only because they may lead (usually after the development of sublabyrinthine empyema) to serious endocranial or, less often, to labyrinthine complications, but because they may result in empyema of the petrosal apex. The author emphasizes that sublabyrinthine empyema is not rare, for it was found in 16 of 62 patients who were operated on in the course of acute otitis media. The author describes the clinical and the histologic aspects of a case

in which the sublabyrinthine empyema caused three perforations into the labyrinth, an extradural abscess, a peribulbar abscess and labyrinthogenic meningitis. In the conclusion he emphasizes once more the necessity of giving careful attention to the sublabyrinthine pneumatic cells.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

HYPERTROPHY OF TONSILS AND BACTERIAL DISEASES. S. PELLER, Monatschr. f. Ohrenh. **70**:851 (July) 1936.

Peller shows the numerical relation between hypertrophy of the tonsils in young persons and the incidence of such diseases as scarlet fever, diphtheria, nephritis, rheumatism, otitis media and appendicitis. Anamnestic investigations revealed to him that young persons with hypertrophy of the palatine tonsils have scarlet fever and diphtheria slightly more often and nephritis and appendicitis much more often than do young persons whose tonsils are not enlarged. Rheumatism and otitis show the same incidence in those with and those without hypertrophy of the palatine tonsils.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

HISTOLOGIC STUDIES ON TONSILS AND ADENOID GROWTHS. E. URBANTSCHITSCH, Monatschr. f. Ohrenh. **70**:1177 (Oct.) 1936.

Urbantschitsch describes the histologic aspects of the tonsils and adenoids removed from 446 patients. All tonsils and adenoids that were histologically examined showed chronic inflammatory changes. In addition, calcareous deposits were discovered 7 times and fungus colonies 33 times. In 25 cases cartilaginous or bony tissues were observed in the tonsillar bed. In 5 cases epithelioid cell tubercles were observed, and subsequent roentgen examination revealed tuberculous processes in the thoracic cavity. Thus the histologic examination of the tonsils and adenoids brought about the diagnosis and early treatment of the tuberculosis. In 2 cases a carcinoma was detected in the tonsils.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

THE RESULTS OF TONSILLECTOMY IN THE JUDGMENT OF THE PATIENTS. H. HABEDANK, München. med. Wchnschr. **83**:1593 (Sept. 25) 1936.

Habedank sent a questionnaire to his patients for the purpose of making a follow-up study after tonsillectomy. The answers indicate the patients' opinions as to the results of the operation. There were 151 replies.

The first question was: "Did the illness or condition for which tonsillectomy was performed disappear, remain the same or become worse?" The replies showed that 50 per cent of the patients were cured, 39 per cent were improved, 9 per cent were unchanged and 2 per cent were worse after the operation.

The second question was: "After tonsillectomy did any new symptoms appear which you think are related to the operation?" New symptoms were reported by 36 per cent of the patients. The symptoms included dysphagia in 4 patients, pharyngitis and infections of the upper part of the respiratory tract in 37, nephritis and pyelitis in 4, rheumatism in 2 and gingivitis, impaired hearing, pain in the solar plexus and cardiac neurosis in 4. However, even though these patients reported various new symptoms, most of them were satisfied with the results of the tonsillectomy because the symptoms from which they had suffered before the operation were worse than their present ones.

The third question was: "Since the tonsillectomy are you more susceptible to colds or do the colds run a different course?" No change in the frequency or character of colds was reported by 44 per cent of the patients; fewer colds were reported by 16 per cent, and 4 per cent stated that they were now free from colds. However, with 36 per cent of the patients colds were more frequent or ran a protracted course.

BRAHDY, Mount Vernon, N. Y.

FIBROMA NASOPHARYNGEUM IN A YOUNG CHILD. J. P. VAN WAASBERGEN, Nederl. tijdschr. v. geneesk. **81**:4163 (Aug. 28) 1937.

An unusual case is described, in which a nasopharyngeal fibroma occurred in a boy aged 6 years. The first symptom was blindness caused by the rapid growth of the tumor. After one month an excrescence of the fibroma presented itself in the left nostril, showing a rapid daily increase and finally lying over the lip. The tumor also caused a swelling of the left eye and slight meningeal irritation. Emaciation and drowsiness increased, and death ensued after nine weeks.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Lungs, Pleura and Mediastinum

PERIVASCULAR PULMONARY CYST: REPORT OF A CASE. JOSE BONABA and JOSE SOTO, Arch. de méd. d. enf. **40**:795 (Dec.) 1937.

A profusely illustrated report is presented of a pulmonary hydatid cyst occurring in a girl aged 10 years. Initial examination revealed clinical signs of corticopleuritis on the right side; in the evolution of the cyst there was rupture, manifested by the usual phenomena of suppuration in this area and demonstrated roentgenographically by the typical appearance of hydatid cyst.

Surgical intervention revealed intense pachypleuritis and an enormous cavity filled with pus and the débris of hydatid membranes. Recovery was slow but complete.

AMESSE, Denver.

PNEUMONIA OF THE MIDDLE LOBE IN AN INFANT OF TWO AND A HALF MONTHS DIAGNOSED BY A LATERAL ROENTGENOGRAM. SIGUIER and GHARIB, Bull. Soc. de pédiat. de Paris **35**:134 (Feb.) 1937.

The title summarizes the case report.

BENJAMIN, Montreal, Canada.

GIANT AIR CYST OF THE LUNG IN A CHILD SIX YEARS OLD. P.-F. ARMAND-DELILLE, J. BOYER and J. HABAS, Bull. Soc. de pédiat. de Paris **35**:238 (April) 1937.

A girl aged 6 years who had had no symptoms of acute illness was thought when examined at school to have a pneumothorax on the right side. After careful roentgenographic investigation, a diagnosis of a balloon air cyst of the lung was made. Iodized poppyseed oil 40 per cent did not enter the cyst from the bronchi.

BENJAMIN, Montreal, Canada.

INTESTINAL HEMORRHAGE IN A CHILD WITH PNEUMONIA: REPORT OF A CASE. M. LAMBRINACOS, Bull. Soc. de pédiat. de Paris **35**:257 (April) 1937.

A boy aged 6 years had melena during the course of pneumonia of the lower lobe of the right lung. A transfusion was given, and he recovered. The possibility of damage to capillaries or even of superficial ulceration of the intestine as a result of invasion by the pneumococcus or its toxin is discussed. Hepatic insufficiency and alterations in the blood have been considered by some to play a role in the production of certain intestinal hemorrhages.

BENJAMIN, Montreal, Canada.

ABSCESS OF THE LUNG FOLLOWING STRANGULATED HERNIA IN AN INFANT TWO MONTHS OLD. H. GRENET and P. AIMÉ, Bull. Soc. de pédiat. de Paris **35**:289 (May) 1937.

A girl who had bilateral inguinal hernia showed strangulation of the hernia on the right side at the age of 7 months. Reduction by taxis was accomplished with difficulty the following day. The infant began to cough that day, and a few

days later abnormal physical signs were noted in the chest at the base of the left lung. A roentgenogram showed a shadow of increased density in this area. About three weeks later some purulent material was observed on the infant's pillow, and it was assumed that this came from the lung. The infant recovered.

BENJAMIN, Montreal, Canada.

ETIOLOGY, PROGNOSIS AND TREATMENT OF EMPYEMA IN CHILDREN. RICARDO S. AGUIRRE, Rev. méd. latino-am. **22**:863 (May) 1937.

The high mortality of empyema occurring in the first two years of life is due to a number of factors, among which are: the existence of concurrent infections, such as otitis media, impetigo and furunculosis, and in the newborn, septicemia; the greater laxity of the mediastinum in early life; the relative frequency with which bronchopneumonia occurs with subsequent bilateral empyema, and the frequency of streptococcic and staphylococcic invasions and the lessened organic defense in early life.

The relative merits of thoracotomy and aspiration for the forms of empyema occurring in infancy are discussed in detail.

DWYER, Kansas City, Mo.

VITAMIN C IN THE TREATMENT OF PNEUMONIA. J. SANDER and W. NIEDERBERGER, München. med. Wchnschr. **83**:2074 (Dec. 18) 1936.

The authors present a chart to show the parallelism between the monthly variation in the frequency of vitamin C deficiency in persons on an average diet and the rate of mortality from pneumonia. Vitamin C deficiency is most prevalent during the winter and spring, reaching a peak in April. The same trend is followed by the number of deaths from pneumonia. It is also shown that vitamin C deficiency is most prevalent in persons over 50 years of age and that the mortality from pneumonia is highest during the same years of life.

As a result of these observations the authors treated a series of patients with pneumonia with preparations of ascorbic acid. When the hypovitaminosis was corrected during the first few days of illness the results were good. However, when huge doses of vitamin C were given on the first day of the illness, so that the deficiency was corrected as quickly as possible, the results were excellent. There was a drop in the temperature, the character of the pulse improved, pain disappeared, and the patient felt much better.

BRAHDY, Mount Vernon, N. Y.

DIRECTED BRONCHOGRAPHY WITH A JOINTED CATHETER. F. STRNAD and A. BEUTEL, Röntgenpraxis **9**:484 (July) 1937.

The second medical clinic of the German University in Prague has for a long time been convinced that the introduction of iodized oil into the bronchial tree is most successfully accomplished by means of a soft rubber catheter which is inserted into the larynx under direct vision. The catheter is then directed into that part of the lung which it is desired to visualize. However, difficulty has been encountered in entering the bronchi of the upper part of the lobe. This obstacle has now been obviated by the addition to the catheter of a movable tip the direction of which can be controlled by a silk thread which passes through the catheter. The device has been found highly satisfactory in practice.

MCCUNE, New York.

INFLUENCE OF AGE, CONSTITUTION AND ENVIRONMENT ON THE GENESIS OF LOBAR PNEUMONIA. R. L. GAMBOURG, Pediatria, 1937, p. 35.

The clinical course of lobar pneumonia indicates a special reaction in children, perhaps of an allergic character, in the pulmonary process. Lobar pneumonia is found mostly among well nourished infants without rickets, offspring of healthy young parents living in good or moderately good environments. Lobar pneumonia

is observed in the same season as is grip, that is, from October to May, and as the histories of the patients often reveal frequent attacks of grip and bronchitis it is possible that repeated infections and repeated encounters with the pneumococcus gradually produce sensitivity, as a result of which an allergic state arises and determines the character of the pulmonary process. McKHANN, Boston.

LOBAR PNEUMONIA. C. DE LANGE, Nederl. tijdschr. v. geneesk. **81**:4785 (Oct. 9) 1937.

In this clinical lecture the author describes a case of lobar pneumonia in which the disease occurred in a girl aged 6 years, complicated by hemorrhagic nephritis, empyema and hemiplegia. The course of lobar pneumonia in childhood and the difficulties of differential diagnosis are discussed.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

A CASE OF MECKEL'S DIVERTICULUM WITH UNUSUAL VASCULAR RELATIONSHIPS. V. DERBES and M. B. HOGE, Anat. Rec. **69**:5 (Aug.) 1937.

In the case reported the diverticulum arose from the ileum, 76 cm. from the ileocecal junction. It was uniform in diameter and was 22 cm. long. The terminal portion was fastened to the umbilicus by a cord. The blood supply for this came from the omphalomesenteric vessels, and these are joined by large branches of the epigastric vessels in the abdominal wall. The histologic picture in general was that of diverticulum of the ileum. SNELLING, Toronto, Canada.

TRICHOBEZOAR. JOSEPH SCHWARTZMAN, J. Pediat. **11**:691 (Nov.) 1937.

Bezoars are accumulations of divers materials which form masses of various shapes in the stomach or intestines of man and of animals. Trichobezoar, or hairball, is the most common type and is found in young girls who have acquired the habit of chewing the ends of their hair. It consists largely of hair with fibers of vegetable matter and food detritus enmeshed in it. While this habit is not associated with mental deficiency, it is believed to accompany some type of neurosis because of the association with it of other factors of nervous instability, such as enuresis and spasm nutans. The stomach is the most frequent locale; the bowels may be the site in relatively rare cases. The trichobezoar usually takes the contour of the stomach. A hard tumor in the upper part of the abdomen, which is usually movable and slightly tender, may be present. There may be mild or severe gastric distress. At times strands of hair may be vomited or passed by bowel. Roentgenographic examination is of great value in diagnosis. A case of trichobezoar in a 2½ year old girl is reported. The child made a good recovery after surgical removal of the hairball. In every operation for hairball, thorough examination of the entire gastrointestinal tract is necessary in order not to overlook hairballs. RAUCH, Cincinnati.

ACUTE APPENDICITIS IN CHILDREN UNDER TWELVE YEARS. ARTHUR N. COLLINS, Minnesota Med. **20**:583 (Sept.) 1937.

The author reviews 200 of his own cases. He finds that the incidence of acute appendicitis tends to increase rapidly after the age of 6 years, so that at the age of 12 it is six times that of the ages of 5 and 6. He finds it to be comparatively rare in the first two years of life. His youngest patient was 1 year of age. In the 200 cases there was a mortality rate of 4.5 per cent. From a study of this group he reached the conclusion that when the patient is a girl under the age of 8 great care should be exercised at operation, as 6 of the 7 children dying in this group were girls. ANDERSON, Minneapolis.

DIAGNOSIS OF APPENDICITIS IN CHILDREN. M. L. CARR, Virginia M. Monthly **64**:38 (April) 1937.

Carr reviews briefly the classic symptoms and signs of appendicitis in children and the diagnostic procedures and makes a plea for early diagnosis as a means of reducing the mortality. STONE, Richmond, Va.

APPENDICITIS AND CHILDREN: REPORT OF A CASE WITH AN INTESTINAL PARASITE. W. P. FRAZER, Virginia M. Monthly **64**:31 (April) 1937.

Symptoms and signs of appendicitis and diagnostic difficulties encountered in children are recited. A colored boy 2½ years old had an attack diagnosed as acute appendicitis. The family refused operation and gave a vermifuge. The next day the child was worse. Operation was performed. The appendix had ruptured, and the peritoneal cavity contained much pus and a dead worm, Ascaris lumbricoides, 6½ inches (198 cm.) long. Recovery followed operation.

STONE, Richmond, Va.

CONGENITAL RECTO-SIGMOID STRICTURE. WILFRED SHELDON and HAROLD EDWARDS, Proc. Roy. Soc. Med. **30**:1192 (Aug.) 1937.

A case of congential rectosigmoid stricture is reported, the patient being a boy aged 4 years. The authors give the medical history of the child from the time of his first admission to the hospital at the age of 4 weeks up to the present.

WILLIAMSON, New Orleans.

INCOMPLETE STENOSIS OF THE PYLORUS IN AN INFANT; PYLOROTOMY; CURE. PAUL GIRAUD, BOURDE and SARDOU, Bull. Soc. de pédiat. de Paris **35**:55 (Jan.) 1937.

A boy aged 2 months, who was athreptic, began to vomit at the age of 2 weeks. Roentgenographic examination showed no obstruction of the pylorus, and clinical signs of stenosis were not observed. The child was treated for five months with little success before pylorotomy was performed. After the operation no more vomiting occurred, and the child recovered. It is pointed out that when athrepsia is due to a mechanical defect the infant's resistance is much better than when it is due to disease; even so, it is advisable not to allow the infant to become repeatedly acutely dehydrated over so long a period as was done in this case before performing this simple and effective operation. BENJAMIN, Montreal, Canada.

ULCERS OF THE SMALL INTESTINE. MICHEL SALMON, Bull. Soc. de pédiat. de Paris **35**:102 (Feb.) 1937.

An Armenian girl aged 14 was operated on after a diagnosis of acute appendicitis had been made. An ulcer of the ileum was found, and the loop of bowel affected was resected; resection was followed by an end to end anastomosis. Recovery was uneventful. Histologically, tubercles were found in some of the sections after repeated search; had one been contented with the first examination of a few sections this lesion would have been classed as a simple ulcer, whereas more careful study revealed its true nature. BENJAMIN, Montreal, Canada.

ABSCESS AT THE HILUS OF THE LIVER WITH UMBILICAL FISTULA IN AN INFANT OF THREE MONTHS: ROENTGENOGRAPHIC DIAGNOSIS WITH IODIZED POPPYSEED OIL; RECOVERY. MARCEL LELONG, P. AIMÉ and JOSEPH, Bull. Soc. de pédiat. de Paris **35**:137 (Feb.) 1937.

A girl aged 3 months had a slight yellowish discharge from the umbilicus which did not heal properly after birth. The liver extended to 3 fingerbreadths below the costal margin, and pressure over it produced an increase in the dis-

charge from the navel. Roentgenographic examination after the injection of iodized poppyseed oil 40 per cent into the fistula showed it to be connected with a pocket at the hilus of the liver. The sequence of events was probably infection of the umbilicus, followed by phlebitis of the umbilical vein with the formation of a periphlebitic abscess at the hilus of the liver, bursting of the abscess into a branch of the hepatic duct and establishment of a communication between the extrahepatic biliary channel and the umbilical vein, which remained patent to the exterior opening at the navel. When the biliary fistula carried the bile out through the navel the stools were light colored, and when the discharge at the navel was scanty the stools were darker. The umbilical discharge disappeared spontaneously. There was no evidence of severe infection at the umbilicus at any time, and a latent period of three months occurred before the biliary connection was manifest. It is important to bear in mind that enlargement of the liver in a young infant may be due to umbilical infection.

BENJAMIN, Montreal, Canada.

INCONTINENCE OF THE ANAL SPHINCTER CAUSED BY A LARGE RECTAL FECALITH. E. SORREL, BRET and ROUGÉ, Bull. Soc. de pédiat. de Paris **35**:350 (June) 1937.

A girl aged 10 had incontinence of feces for about two months. There was no incontinence of urine. There was a history of mild constipation. The anal sphincter was intact but was kept open by a large hard mass of feces around which liquid feces escaped continuously from the rectum. With the patient under general anesthesia most of the mass was removed, and purgatives and enemas were given thereafter. The condition was cured after three days. When seen repeatedly at later dates the child was well.

BENJAMIN, Montreal, Canada.

THE VALUE OF THE TAKATA-ARA-JEZLER REACTION. URBANO FREITAS and JOSE SOBRINHO, J. de pediat., Rio de Janeiro **4**:384 (Sept.) 1937.

In a study of 80 cases of varying degrees of jaundice the authors believe that this test was of value in differentiating obstructive jaundice from hepatic lesions. The result is usually positive in cases of tuberculous involvement of the liver and usually negative in cases of syphilitic involvement.

SANFORD, Chicago.

MESENTERIC CYST FORMATION IN AN INFANT. L. RAUTER, Med. Klin. **33**:1402 (Oct. 15) 1937.

Rauter describes a case of mesenteric cyst, the patient being an infant 1¾ months old. The symptoms were those of ileus. At times a fluctuant, mobile tumor about the size of a hen's egg could be palpated just below the umbilicus. The infant's general condition was poor, and death due to meningitis secondary to bilateral purulent otitis media occurred on the tenth day after the operation.

SIEMSEN, Chicago.

THE CHOLESTEROL METABOLISM IN GLYCOGEN STORAGE DISEASE. H. BEUMER, München. med. Wchnschr. **84**:1007 (June 25) 1937.

Beumer discusses a case in which a disturbance in glycogen storage complicated by xanthomatosis occurred in a 9 year old boy. The cholesterol metabolism was studied in detail. The values for cholesterol in the serum varied from 457 to 700 mg. per hundred cubic centimeters. The cholesterol content of the serum was independent of the diet, whether this was poor or rich in cholesterol. The cutaneous lesions and the enlargement of the liver were not influenced during a period of three months when the diet was free from cholesterol and fat. Beumer concludes that the xanthomatosis and the glycogenesis were independent of alimentary influences but were due to some endogenous disturbance in cholesterol metabolism.

BRAHDY, Mount Vernon, N. Y.

Nervous Diseases

TUMOR OF THE BRAIN WITH NORMAL ENCEPHALOGRAM. N. SAVITSKY and M. B. BENDER, Am. J. M. Sc. **194**:96 (July) 1937.

A group of 9 cases of tumor of the brain in which the encephalograms were normal are reported. A negative aerogram does not exclude tumor of the brain, particularly one in the early stages. Normal ventricular and subarachnoid spaces may exist in spite of the location, nature or duration of the tumor.

HENSKE, Omaha.

ARTIFICIAL FEVER TREATMENT OF CHOREA. C. H. BARNACLE, J. R. EWALT and F. G. EBAUGH, J. A. M. A. **109**:111 (July 10) 1937.

Forty-five patients with Sydenham's chorea were treated by producing in them an artificial fever by means of the Kettering hypotherm. Maintenance at from 105 to 105.4 F. (rectal) for two and one-half hours was found effective. The average number of treatments was 12.6; the average number of hours of fever, 32.9; and the average duration of treatment, 22.3 days. The immediate results were excellent. There have been four recurrences. Most of the patients have been followed up, and the results of their treatment have been found lasting. Carditis, which occurred in 42.2 per cent, did not interfere with the treatment.

BONAR, Salt Lake City.

IS THERE A PHYSIOLOGIC CATALEPSY IN INFANTS? H. BARUK, Bull. Soc. de pédiat. de Paris **35**:83 (Feb.) 1937.

Catalepsy is a psychomotor disturbance in which there is absence of motor initiative with active adoption of positions imposed from without and maintenance of them for a greater or lesser time. It is a form of catatonia, which also includes negativism, in which muscular stiffness is so marked as to resist all movement. When the latter condition is present, it is usually accompanied by vasomotor disturbances such as salivation. It is not definitely established what part of the cerebrum plays a role in the production of this condition; a cortical and a basilar involvement have been advanced in two theories, respectively. Experimentally, the condition has been produced in higher vertebrates, such as the cat, the monkey and birds by injections of toxic substances such as bulbocapnine and bile, obtained in some cases by duodenal drainage; similar injections into fish and reptiles have failed to produce any signs of catatonia. With bulbocapnine in animals with ablation of the cortex, the results have been contradictory. Because of the low level of function of the cortex in young infants, it was thought that if the condition were observed in them it might add weight against the theory which postulates cortical disturbance in the production of the condition. Over many years of study no infants were observed with true catalepsy, so that no light was shed on this difficult neuropsychiatric problem.

BENJAMIN, Montreal, Canada.

POLYRADICULONEURITIS WITH ALBUMINOCYTOLOGIC DISSOCIATION OF THE SPINAL FLUID (SYNDROME OF GUILLAIN AND BARRÉ). P. GIRAUD and J. BOUDOURESQUE, Bull. Soc. de pédiat. de Paris **35**:297 (May) 1937.

Two girls, one 2 years old and the other 3 years old, had infectious polyneuritis. Both recovered completely after two months and six weeks, respectively. The spinal fluids showed a high albumin content with few cells, and there was a progressive decrease of albumin in these spinal fluids which paralleled the clinical improvement. This condition has been observed as a sequela of infection of various types but the point of view expressed is that there is probably a specific etiologic origin.

BENJAMIN, Montreal, Canada.

PRIMARY PURULENT MENINGITIS DUE TO HEMOLYTIC STREPTOCOCCUS CURED BY PARA-AMINOPHENYLSULFAMIDE. R. MARTIN and A. DELAUNAY, Bull. Soc. de pédiat. de Paris **35**:382 (June) 1937.

A boy 8½ years old had rhinopharyngitis, and purulent meningitis developed without otitis or mastoiditis. He was treated with antimeningococcic serum, at first without any improvement. A culture of the spinal fluid revealed hemolytic streptococci, type B. Sulfanilamide was administered orally, beginning with a daily dose of 1.5 Gm., increasing the dose to 3 Gm. and then gradually decreasing the dose until the administration of the drug was stopped, two weeks after the first dose was given. The boy showed improvement shortly after this medication was begun and made a complete recovery. The facts that the streptococcus took a long time to grow when isolated from the spinal fluid and that it was necessary to inject intraperitoneally 0.5 cc. of ascitic broth culture into a 20 Gm. rat to kill it in twenty-four hours indicate possibly that the organism was not highly virulent.

BENJAMIN, Montreal, Canada.

THE START REFLEX IN CHILDREN WITH LITTLE'S DISEASE. M. P. R. BIZE, Rev. neurol. **67**:109 (Jan.) 1937.

Bize presents 2 cases of Little's disease in which an exaggerated start reflex was shown. He points out that the reflex is primarily constitutional but that as emotional control develops, the reflex becomes conditioned. This inhibition does not develop in infants with Little's disease, probably because of an anatomic lack.

DAFFINEE, Boston.

EXPERIMENTAL STUDY ON THE ETIOLOGY OF ENCEPHALITIS IN CHILDREN. MARTA RADICI, Riv. di clin. pediat. **35**:289 (April) 1937.

Lumbar punctures were done on 21 children. Of these, 5 had chorea, 7 had sporadic encephalitis and 9 had postinfectious encephalitis. The cerebrospinal fluid was instilled into the corneas of rabbits; in each rabbit a dendritic or a punctate keratitis appeared, and death from encephalitis usually followed. The material recovered from the eyes showing the dendritic and punctate keratitis was used to inoculate other rabbits with the same condition. Similar tests with the cerebrospinal fluid of 70 other children with pathologic conditions of the central nervous system, but not with chorea or encephalitis, gave negative results.

The instillation of material from human herpetic vesicles into the corneas of rabbits resulted in herpetic keratitis but not in dendritic or punctate keratitis. Similar tests with cerebrospinal fluid from persons with febrile herpes did not result in any reaction. The instillation into the corneas of rabbits of blood serum, urine, fecal filtrates and bacterial cultures obtained from the aforementioned children gave negative results.

HIGGINS, Boston.

MIXED INFECTION OF THE MENINGES CAUSED BY KOCH AND FRIEDLÄNDER BACILLI. I. MÓRITZ, Orvosi hetil. **81**:603 (June 5) 1937.

A 4 month old infant was admitted to the pediatric clinic in Budapest with meningeal symptoms; besides this it had otitis media in both ears. The first lumbar puncture showed clear cerebrospinal fluid with increased pressure. The Pandy test was positive; protein content was 1.7 mg. per hundred cubic centimeters; the cell count was 110; the sediment was chiefly mononuclears; the culture showed pneumobacilli (Friedländer type). The Mantoux test was positive. The roentgen examination of the lungs showed miliary tuberculosis. The lumbar puncture was repeated later three times and Friedländer bacilli were found twice. The cerebrospinal fluid later became slightly opalescent, but the last puncture again showed a clear fluid, in which tubercle bacilli were found. The postmortem examination revealed at the base of the brain a greenish-yellowish seropurulent exudate, with tubercles in the sylvian fissure.

Probably the first infection was that of the tuberculous meningitis, and the Friedländer bacilli came later from the otitis. Friedländer bacilli were also found in the purulent secretion of the ears. It is interesting that the cerebrospinal fluid was almost always clear and that the sediment showed mostly mononuclears and that in spite of this Friedländer bacilli could almost always be cultured.

GÖTTCHE, Budapest, Hungary.

THE PRESSURE OF CEREBROSPINAL FLUID AND ITS SIGNIFICANCE FOR PHYSIOLOGY. A. VERJAAL, Nederl. tijdschr. v. geneesk. **81**:3432 (July 17) 1937.

In the horizontal position, the pressure of the cerebrospinal fluid at all levels is about equal to 15 cm. of fluid. In the vertical position, the pressure is 45 cm. at the lumbar level, and just below the cranial vault it is about minus 20 cm. This peculiar behavior of the pressure when the position of the body is changed is caused by the fact that the walls of the dural space are partly rigid and partly elastic. The elastic wall is formed by the epidural space in the vertebral canal. On compression of the jugular veins the pressure rises through an increase of the contents of the dural space; increased abdominal pressure makes the pressure rise, mainly by limiting the volume of the intradural space. In every position of the body the distribution of the liquor pressure is such that the pressure gradient between the central nervous system and the heart is the same everywhere, about 15 cm. of water, which guarantees a constant drainage of venous blood.

VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

DISCLOSURE OF FOSTER-PARENTAGE TO A BOY. SIDNEY TARACHOW, Am. J. Psychiat. **94**:401 (Sept.) 1937.

The author presents a discussion of behavior disorders and other psychologic problems resulting from late disclosure of foster parentage. Seven boys, residents at the New York State Training School for Boys, are analyzed. The asocial behavior of each had its immediate origin in the fact that the boy's information on his true origin came late. Though in each instance these boys had a vague idea of their status, definite information had been withheld until the thirteenth or fourteenth year. The outstanding symptoms presented by this group of boys were truancy, stealing and running away from home.

Resentment toward the foster parents was not a prominent factor.

JAHR, Omaha.

CORRELATIONS OF BEHAVIOR AND NEUROPATHOLOGY IN A CASE OF CEREBRAL PALSY FROM BIRTH INJURY. ARNOLD GESELL and HARRY M. ZIMMERMAN, Am. J. Psychiat. **94**:505 (Nov.) 1937.

Gesell and Zimmerman present a most interesting report of a boy who suffered a cerebral injury at birth and who died of appendicitis at the age of 14. Autopsy revealed an uncomplicated lesion of the basal ganglions, of the status marmoratus type. The child's psychologic development and his behavior characteristics were studied by repeated observations, cinema records and a training program from the age of 4 years until his death. From these detailed studies and their correlation with the observations at autopsy, the authors conclude that "the blemish of behavior patterning is not commensurate with the destruction of the primary sensory and motor mechanisms. Mental growth tends toward an optimum organization."

No abstract can do the paper justice. It is a classic to be fully appreciated only in the original.

JAHR, Omaha.

THE BEHAVIOR OF CHILDREN TAKING BENZEDRINE. C. BRADLEY, Am. J. Psychiat. **94**:577 (Nov.) 1937

Twenty-one boys and 9 girls (residents at the Emma Bendleton Bradley Home) suffering from various behavior anomalies were given from 10 to 30 mg. of benzedrine sulfate daily, and their reactions were carefully observed. Two showed intolerance to the therapeutic dose. In the others improvement, particularly in the performance of school work, was spectacular. A large percentage showed emotional improvement, without, however, losing interest in their surroundings.

JAHR, Omaha.

CHILD ANALYSIS AS A TECHNIQUE IN THE INVESTIGATION OF MENTAL MECHANISMS, ILLUSTRATED BY A STUDY OF ENURESIS. MARGARET W. GERARD, Am. J. Psychiat. **94**:652 (Nov.) 1937.

Six patients with nocturnal enuresis were psychoanalyzed, 3 boys and 3 girls. These children all showed a characteristic emotional pattern, different from the pattern found in children presenting other difficulties. Enuresis had developed in all these children after the fifth year, and factors which could otherwise explain bedwetting (slovenly training, organic defects or jealousy) were excluded.

The boys were retiring and self deprecatory; they were afraid of physical pain and therefore averse to any form of rough play. They were generally slow and dawdling in all their routine activities, demanding more than the average amount of help in performing daily tasks. Scholastically they were poor and of the day-dreaming variety. The girls presented a complete contrast to this picture. They were active and independent; they exerted leadership among the girls and were proficient in their tasks. Scholastically they presented no problem. Play indulged in with boys showed a strongly competitive spirit, associated with a depreciation of the boys. Unlike the boys, who were generally evasive, secretive and untruthful, the girls were frank and honest in their relationship with other persons. The boys, on the whole, behaved as though they felt inferior to their fellows, whereas the girls behaved as if they were equal or even superior to theirs. In both sexes a real anxiety was apparent, which expressed itself as nocturnal fears.

Analysis of the boys indicated fear of women as dangerous persons capable of destruction if the boy were active. In overcoming this fear the child associated himself with passive female, and with a negation of active male, characteristics. Enuresis was his passive pattern, the urine flowing out uncontrolled, and the boy being irresponsible. For the girl, man is the destructive aggressor, with capacity for injury. In her attempt to eliminate him from her fantasies she associates herself with the active male, instead of with the passive female, characteristics. Enuresis to her is an active soiling rather than a passive flow.

In each of these 6 cases improvement or cessation of enuresis occurred after psychoanalytic treatment.

JAHR, Omaha.

CHILD PSYCHIATRY. JAMES PLANT, Am. J. Psychiat. **94**:665 (Nov.) 1937.

This article contains a plea for proper understanding of the nature of the child, his physical, intellectual and social capacities and limitations, and the pressures imposed on him by his environment.

JAHR, Omaha.

SOME THERAPEUTIC PRINCIPLES APPLICABLE TO PSYCHIATRIC WORK WITH CHILDREN. FREDERICK H. ALLEN, Am. J. Psychiat. **94**:671 (Nov.) 1937.

This paper deals with a discussion of growth experiences and their attendant fears. In his development the child is confronted with the inevitable process of growing up and thereby losing maternal support. Therapy involves helping the child to find a creative use of his own potentialities so that he may "catch up with himself" and bring himself face to face with reality.

JAHR, Omaha.

PHYSICAL EDUCATION PROGRAM FOR MENTAL DEFECTIVES. E. ARTHUR WHITNEY and MARY MCD. SCHICK, M. Rec. **146**:124 (Aug. 4) 1937.

The authors give an outline of a physical education program for boys and one for girls, carried out at the Elwyn school for mentally retarded children. A few case histories showing the improvement of the children are included. The authors, in concluding, state that physical education has a place of distinct value in the field of mental deficiency. An adequate program does not require elaborate equipment but does require trained workers who can see and feel the value of their endeavors. The program of physical education at the Elwyn school has improved the posture of the children, developed character and personality, developed better habits, increased generally the mental acuity of the children and advanced the standards of citizenship at Elwyn. WILLIAMSON, New Orleans.

PSYCHIATRIC TREATMENT IN AN INSTITUTION. SAMUEL Z. ORGEL, New York State J. Med. **37**:1141 (June 15) 1937.

Orgel gives a detailed report of a 9 year old psychoneurotic boy who became so uncontrollable and destructive at home that he had to be placed in an institution. After a complete psychiatric study of the grandparents, parents and siblings, it was possible to establish a course of successful psychiatric treatment.

AIKMAN, Rochester, N. Y.

BORDERLINE TESTS. THEODORE HELLER, Ztschr. f. Kinderpsychiat. **4**:7 (May) 1937.

A series of practical tests for children is outlined in chronologic order, beginning with the age of 3 years and including the fourteenth year. The pediatrician who is unequipped to give the child a quantitative psychologic examination may employ these tables and gain a fair idea as to the approximate mental status of his young patient.

JAHR, Omaha.

Diseases of the Genitourinary Tract

INFECTIONS OF THE URINARY TRACT DUE TO BACTERIUM DYSENTERIAE. ERWIN NETER, J. Infect. Dis. **61**:338 (Nov.-Dec.) 1937.

"It follows from the reports of 14 cases collected from the literature and my own observations, that dysentery bacilli may cause an acute infection of the urinary tract. This may happen during or following an attack of intestinal dysentery, or as in my cases, in patients without history or clinical evidence of dysentery."

TOOMEY, Cleveland.

THE USE OF SULFANILAMIDE AS A URINARY ANTISEPTIC. HENRY F. HELMHOLZ, J. Pediat. **11**:243 (Aug.) 1937.

Helmholz has found sulfanilamide of great therapeutic value as a urinary antiseptic. It is bactericidal for most organisms which cause infection of the urinary tract. It is therapeutically active in certain conditions in which the other urinary antiseptics have failed. It has been used successfully in the acute stage of disease of the urinary tract; it is active in alkaline urine, and it has been successfully used in cases of renal insufficiency. The dose necessary to produce bactericidal urine is considerably less than doses which have been given without any ill effects for infections due to streptococci. One further advantage of sulfanilamide over the other urinary antiseptics is the ease of its administration. Certain organisms, notably Streptococcus faecalis, are resistant to its action.

RAUH, Cincinnati

MALIGNANT TUMOR OF THE OVARY OCCURRING IN A THIRTEEN YEAR OLD GIRL. ALEXANDER A. LEVI, New England J. Med. **217**:595 (Oct. 17) 1937.

Lanman reports 5 cases of ovarian tumor in children under the age of 12 in a total of 12,260 patients admitted to the surgical service at the Children's Hospital, Boston, during a ten year period.

It is apparent that although malignant tumors of the ovary do occur in children, they are extremely rare.

Levi's patient was a 13 year old white girl. She had never menstruated. She was sitting in a chair with her legs hanging over its arm when she suddenly noticed a sharp pain in the right lower quadrant of the abdomen. About an hour later she went to bed, but was awakened after about two hours of sleep by severe pain in the same region. Shortly afterward she vomited; she was then seen by a physician, who found spasm and tenderness in the right lower quadrant of the abdomen, a normal temperature and a pulse rate of 90.

Rectoabdominal examination disclosed the cervix and uterus to be infantile in type. The left vault was normal; in the right vault could be palpated a tender, freely moveable firm mass the size of a hen's egg.

When the peritoneum was incised about 250 cc. of blood was immediately discharged from the abdominal cavity. The right ovary was firm, about three quarters of the size of a large hen's egg, and was ruptured for a distance of about two thirds of its diameter. In the V-space of the rupture, a blood clot had accumulated; in this region there was also present a yellow, rubber-like material. The ovary was removed. Examination of both fallopian tubes, the uterus and the left ovary disclosed no abnormalities. The peritoneum, the bladder and all visible parts of the intestine appeared normal. The appendix, buried in adhesions (except the tip, which was bulbous and appeared inflamed), was removed.

The pathologic diagnosis was carcinoma simplex of the ovary.

The immediate postoperative course was uneventful, and the patient left the hospital on the ninth day after the operation.

Roentgenograms were taken of the lungs, the heart, the kidneys, the ureters, the bladder, the abdomen, the lumbosacral spine, the pelvis and the hips. No abnormal shadows were found.

The patient received high voltage roentgen irradiation followed by a course of seventeen exposures.

Seventeen months after the operation the patient had improved in general health, had gained weight and had continued with her daily school work and physical activities. She had not yet menstruated.

GENGENBACH, Denver.

SARCOMA OF GLANS PENIS. ALI PASHA IBRAHIM, J. Egyptian M. A. **20**:602 (Dec.) 1937.

A case of spindle cell sarcoma of the glans penis is reported, the patient being a boy 22 months old. There was involvement of the regional lymph nodes. Radium therapy effected rapid improvement in fifteen days and is to be repeated.

MULHERIN, Augusta, Ga.

BACILLUS COLI INFECTIONS OF THE URINARY TRACT. V. VERMOOTEN, South African M. J. **11**:767 (Nov. 13) 1937.

Although acute infections of the kidney or of the pelvis of the kidney are generally associated with fever, urethritis and cystitis are not. Dysuria and also frequency and urgency of urination are symptoms of trigonitis and urethritis and not of pyelitis or cystitis. In order to diagnose a Bacillus coli infection of the urinary tract it is necessary to demonstrate B. coli in the stained smear of the centrifugated urine deposit as well as on culture. In well conducted laboratories the cultures will give incorrect information in over 30 per cent of instances. In

regard to treatment, postural drainage (supine position with the buttocks elevated above the level of the shoulders so that any ureteral kinks or angulations are prevented) and a large fluid intake are more important than any medication. The newer bactericidal drugs are most useful but should be employed with great caution and only in properly selected cases, as they are specific for certain organisms. Methenamine must not be forgotten, as it is still a valuable drug. Existing mechanical defects in urinary drainage must be recognized and removed if infection of the urinary tract is to be successfully treated. GONCE, Madison, Wis.

THE TREATMENT OF PYURIAS OF INFANTS BY RUBIAZOL. HURMUZACHE and I. PRONCENCO, Bull. Soc. de pédiat. de Iasi **7**:90 (Oct.-Dec.) 1936.

The authors treated pyelitis successfully in 5 cases with the average dose of 25 cg. of rubiazol (the hydrochloride of 4-sulfamido-2′: 4′-diaminoazobenzene) per day for a period of ten days. In 4 of the cases the disease was due to colon bacillus infection and in 1 to a proteus infection. LESLIE, Evanston, Ill.

TORSION OF A DERMOID CYST OF THE OVARY SIMULATING PELVIC APPENDICITIS IN A CHILD TWENTY-SIX MONTHS OLD. PIERRE DELTHIL, Bull. Soc. de pédiat. de Paris **35**:69 (Jan.) 1937.

The title summarizes the case report. The preoperative diagnosis was pelvic appendicitis. BENJAMIN, Montreal, Canada.

SEVERE HYPERTENSIVE NEPHRITIS ON THE TWENTY-FOURTH DAY AFTER THE ONSET OF SCARLET FEVER. ROBERT BROCA, FONTAINE and PHILIPPE SERINGE, Bull. Soc. de pédiat. de Paris **35**:326 (June) 1937.

A boy aged 10 had hypertension, convulsions, blurred vision and albuminuria twenty-four days after the onset of scarlet fever. Treatment consisted of bleeding and a dry diet. The possibility of confusing nephritis with encephalitis in such a case is mentioned. Lumbar puncture was not performed. A year later the child was well, and a test of the function showed it to be normal.

BENJAMIN, Montreal, Canada.

TREATMENT OF NOCTURNAL ENEURESIS WITH INJECTIONS OF SOLUTION OF ANTERIOR PITUITARY. ALVARO BAHIA and JOSE PEROBA, Pediat. e puericultura **6**:39 (May) 1937.

Intramuscular injections of a solution of anterior pituitary were used in 8 cases of nocturnal eneuresis. Four patients were cured, 3 were improved, and the condition of 1 was unchanged. SANFORD, Chicago.

THE ETIOLOGY AND DIAGNOSIS OF PERINEPHRITIC ABSCESS. V. HORMUTH, Fortschr. a. d. Geb. d. Röntgenstrahlen **55**:277 (March) 1937.

In some cases the existence of a perinephritic abscess can be demonstrated roentgenographically before operation. The fact that this is possible implies the presence of a fistulous communication between the pelvis and the abscess cavity. Such a communication is most commonly associated with kidney stones. Obfuscation of the shadow of the psoas muscle is a highly important roentgenographic sign of perinephritic abscess; absence of this sign is sufficient ground for ruling out the existence of such a lesion. Lack of definition of the kidney shadow and diffuse enlargement of the kidney also point to abscess. The diaphragm is sometimes elevated on the affected side. Scoliosis is an inconstant finding. MCCUNE, New York.

VISUALIZATION OF THE RENAL CAPSULE AFTER RETROGRADE PYELOGRAPHY IN A PATIENT WITH CHRONIC PYELITIS AND PERINEPHRITIS. H. E. BÜTTNER and T. CELLARIUS, Röntgenpraxis **9**:400 (June) 1937.

Attention is drawn to the fact that contrast mediums injected into the ureters during the course of acute suppurative diseases of the kidney may penetrate the viscus and escape into the perirenal tissues. An illustrative case is reported. References are supplied to the clinical and to the experimental literature.

McCUNE, New York.

NEPHROLITHIASIS AND CHOLELITHIASIS IN CHILDREN. A. ZAMBALOS, Röntgenpraxis **9**:416 (June) 1937.

A Greek child aged 14 complained of discomfort in the right renal region since the age of 3½ years. Roentgen examination revealed a kidney stone on the right side and a small concretion in the gallbladder. The latter had not given rise to symptoms.

McCUNE, New York.

PRIMARY ACTINOMYCOSIS OF THE KIDNEY. C. W. PRINS, Nederl. tijdschr. v. geneesk. **81**:3652 (July 31) 1937.

The term primary actinomycosis of the kidney is theoretically incorrect but clinically justifiable on the lines which are indicated in this paper. Considering the literature on this basis, the author concludes that in only 9 of the 19 reported cases was the condition true primary actinomycosis, a case of his own in a girl aged 2 years being included. From the symptoms in these cases a synthesis of the clinical picture is attempted. A discussion of the therapy is included.

VAN CREVELD, Amsterdam, Netherlands.

CARBUNCLES OF THE KIDNEY. D. S. BARTSTRA, Nederl. tijdschr. v. geneesk. **81**: 5612 (Nov. 20) 1937.

Three cases of carbuncle of the kidney are reported. All the lesions healed, 2 without operation, while in the third case, that of a girl aged 14, one enlarged kidney was removed. The author discusses the roentgenographic signs, especially those of the conservatively treated carbuncles. In the pyelogram signs of the inflammatory swelling of the kidney were prominent features. A filling defect was not seen.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Ductless Glands; Endocrinology

INDUCTION OF PENILE ERECTION BY MALE HORMONE SUBSTANCES. JAMES B. HAMILTON, Endocrinology **21**:744 (Nov.) 1937.

Androgens produce growth, maintenance and function of the male reproductive tract. Function includes erectile ability.

Immature animals were given injections of androgenic substances, testosterone acetate and testosterone propionate, which stimulated penile growth and erection. Castration and hypophysectomy of adult rodents appeared to result in regressive changes of the penis and diminution of erectile properties. Administration of androgens to castrated and hypophysectomized male rodents resulted in the maintenance of erectile capacity.

Injections of testosterone propionate in 5 immature children, in a 27 year old man with hypopituitarism and in a 43 year old man who had complete impotence of eight years' duration resulted in the production of erections, which in some cases approached a state of priapism.

The value of androgens in cases of hypogenitalism and impotence is suggested.

JACOBSEN, Buffalo.

THE EFFECT OF TESTOSTERONE, TESTOSTERONE PROPIONATE AND DEHYDROANDROSTERONE ON THE SECRETION OF THE GONADOTROPIC COMPLEX AS EVIDENCED IN PARABIOTIC RATS. ROY HERTZ and ROLAND K. MEYER, Endocrinology **21**:756 (Nov.) 1937.

The ovarian hypertrophy which occurs when an immature female rat is put into parabiosis with a castrated male or female litter mate is employed as a quantitative measure of the level of hypophysial gonadotropic secretion.

Data are presented from observations on 114 pairs in which the gonadectomized partner was treated with varying doses of testosterone, testosterone propionate and dehydroandrosterone.

It is concluded that: (1) The administration of adequate doses of these substances to the castrated partner completely inhibits the ovarian hypertrophy usually observed in the normal partner, and the degree of ovarian hypertrophy progressively increases as the dose of androgen is reduced; (2) larger doses of testosterone are required for inhibition in castrated male-female pairs than in castrated female-female pairs, and (3) on a weight-for-weight basis, the relative capacity of these three androgens to inhibit pituitary gonadotropic secretion is in the same order as their respective androgenic potencies, testosterone propionate being most effective and dehydroandrosterone least effective. Nevertheless, equally inhibitory dosages of the three respective androgens do not produce comparable seminal vesicle weights.

JACOBSEN, Buffalo.

EFFECTS OF THE THYROTROPIC HORMONE OF THE ANTERIOR PITUITARY IN MAN. E. F. SCOWEN, Lancet **2**:799 (Oct. 2) 1937.

Scowen bases his report on a study of 11 patients, all adults. Two showed no evidence of endocrine abnormality; the pituitary glands of 3 had been destroyed by tumors, and 6 had classic myxedema.

Thyrotropic substance prepared from the anterior lobe of the pituitary gland of the pig raised the metabolic rate for healthy persons and for persons with pituitary insufficiency but was without effect in the presence of myxedema.

LANGMANN, New York.

CONGENITAL GOITER. RHENTER and P. MAGNIN, Bull. Soc. d'obst. et de gynéc. **26**:727 (Nov.) 1937.

The mother of the infant described was 34 years of age and had a large parenchymatous goiter, with no other clinical signs of thyroid disease. The goiter had been present for some time. There was no family history of the disease. The child, a boy, weighed 4,630 Gm. at birth. He had a large swelling of the thyroid, involving both lobes; this was apparently a goiter of the same type as that of the mother. The tumor caused the infant considerable difficulty; there were cyanosis and paroxysms of dyspnea. Surgical intervention was considered but was postponed. The symptoms gradually diminished during the first few days, and at the end of four days the circumference of the neck, which had been 30 cm. at birth, was reduced to 28 cm. A roentgenogram of the thorax showed no abnormality. At the age of 13 days the child was discharged, apparently in good condition. The goiter had shown no increase in size.

GLASER, Rochester, N. Y.

EARLY OBSERVATIONS ON THE DEVELOPMENT OF THE PENIS IN CHILDREN FOLLOWING INJECTIONS OF TESTOSTERONE ACETATE AND PROPIONATE. P. MORICARD and P.-R. BIZE, Bull. Soc. de pédiat. de Paris **35**:26 (Jan.) 1937.

Ten boys with genital hypoplasia were observed for from two to eight months, during which period they were given injections of testosterone, usually two a week. Increases in the length and circumference of the penis were noted. The

testicles actually diminished in size in some cases. Growth of height and weight was accelerated. In those who were obese, diminution of adiposity of the breast occurred. Growth of pubic hair was accelerated.

BENJAMIN, Montreal, Canada.

PSYCHIC CHANGES FOLLOWING INJECTIONS OF TESTOSTERONE IN YOUNG BOYS. P.-R. BIZE and R. MORICARD, Bull. Soc. de pédiat. de Paris **35**:38 (Jan.) 1937.

A small group of boys who were given injections of testosterone over a period of months showed changes in personality as well as physical modifications. The latter were reported in a previous communication; the former consisted of an impression of increased strength and intellectual curiosity. Especially, there was increased aggressiveness, shown by a detachment from the family group and a greater tendency to assertiveness. There was no definite modification of sexual experience for any of the boys.

BENJAMIN, Montreal, Canada.

PHLEGMON OF THE THYMUS. MARCEL LANGLOIS and ROLAND THIBAUDEAU, Bull. Soc. de pédiat. de Paris **35**:261 (April) 1937.

A premature, poorly nourished girl was admitted to the hospital at the age of 2 months because of digestive disturbance. She improved under suitable treatment. At the age of 5 months she had bilateral acute suppurative otitis media; about three weeks later she became very ill, and a swelling was noted at the jugular notch. Roentgenographic examination revealed a large area of density in the region of the thymus. She became progressively worse and died of suffocation a few days later. No exploration of the swelling which bulged just above the manubrium was attempted. Necropsy revealed a large abscess of the thymus from which a culture of streptococci was obtained.

BENJAMIN, Montreal, Canada.

ADIPOSOGENITAL SYNDROME AND PIGMENTARY RETINITIS (SYNDROME OF BARDET-LAURENCE-BIEDL). P. PESME and G. HIRTZ, Rev. d'oto-neuro-opht. **15**:257 (April) 1937.

The case reported is that of a boy aged 8½ years with an adiposogenital syndrome, visual acuity of 1/10 in each eye and pigmentary retinitis. The patient's mother was obese and had signs of insufficiency of the anterior lobe of the hypophysis and sympathicotonia. The patient weighed 40 Kg. and was 130 cm. in height. Under treatment with extract of the anterior lobe of the hypophysis and with thyroid, adrenal and whole pituitary, followed by the administration of extract of embryonal tissues, a marked improvement in the condition occurred. There were no signs of malformation of the skeletal system or the sella turcica. The sugar tolerance was normal. There was no polyuria, lymphocytosis or disturbance in thermogenesis or metabolism. Opinions vary as to the relation of the retinitis and the adiposogenital syndrome. Zondek expressed the belief that the retinal changes were the result of dysfunction of the hypophysis, an opinion which Pesme and Hirtz think is substantiated by the following facts: The visual cells and the nervous portion of the hypophysis are derived from the cells lining the medullary groove. There are anatomicophysiologic relations between the retina and the hypophysis by way of the tangential nucleus of the hypothalamic region. Excitation of the retina brings about a specific secretion of the hypophysis which acts on the chromatophores and testes of the duck.

DENNIS, Wagon Wheel Gap, Colo. [ARCH. NEUROL. & PSYCHIAT.]

MALIGN TERATOID TUMOR IN THE HYPOPHYSIAL REGION. V. A. JENSEN, Acta ophth. **15**:193, 1937.

In a 13 year old girl lack of appetite, emaciation, headache, drowsiness, vomiting, pareses of the ocular muscles and bitemporal hemianopia developed. In the

course of a short time papillary stasis and involvement of other cranial nerves appeared. A roentgenogram revealed destruction of the sella turcica. The patient died after two and one-half months, and autopsy revealed a large interpeduncular tumor, with extension into one sphenoid sinus and both orbits. Histologic examination showed a teratoid tumor. There are two photographs of the tumor but no photomicrographs.

O. P. PERKINS. [ARCH. OPHTH.]

HYPOPHYSIAL CACHEXIA IN A GIRL OF TWELVE YEARS. A. G. SCHOO, Maandschr. v. kindergeneesk. **6**:453 (Aug.) 1937.

A description of a probable case of hypophysial cachexia in a girl aged 12 years is presented. The disease was thought to have started four years previously. The girl showed a decreased basal metabolic rate and an abnormal blood sugar curve with extreme hypoglycemic values. Notwithstanding treatment with ambinon and thyroid preparations the girl grew worse and finally died. Autopsy was not done.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Muscles, Bones, Joints and Lymph Glands

SERUM PHOSPHATASE ACTIVITY IN GENERALIZED OSTEOSCLEROSIS DUE TO CHRONIC FLUORINE INTOXICATION IN MAN. K. ROHOLM, A. B. GUTMAN and E. B. GUTMAN, Proc. Soc. Exper. Biol. & Med. **37**:376 (Nov.) 1937.

A peculiar form of generalized osteosclerosis occurs in workers exposed to the dust of cryolite, a fluorine compound (Na_3AlF_6). There is a diffuse increase of density in the bones, particularly in the spine, pelvis and ribs, with calcification of the tendinous insertions of muscles and ligaments. The spine and thoracic cage become rigid, and vague "rheumatic" pains develop. The sclerosed bones weigh three times the normal weight and are brittle. The fluorine content is ten times normal. The serum phosphatase, the serum calcium and the serum inorganic phosphorus were all normal in value in the 20 cases examined.

HANSEN, Minneapolis.

ACUTE OSTEOMYELITIS IN CHILDREN. W. P. BLOUNT, Wisconsin M. J. **36**:910 (Nov.) 1937.

Tuberculosis of the bone is decreasing while osteomyelitis is coming into greater prominence. The axiom "Once an osteomyelitis always an osteomyelitis" is still largely true. In treatment hope lies in preventing the osteomyelitis from becoming chronic. Treatment has changed from heroic radical surgical operation to drainage and rest.

There are two types of osteomyelitis in children: (1) primary hematogenous osteomyelitis, associated with bacteremia, and (2) secondary osteomyelitis, following injury.

That following local injury and contamination may largely be prevented and successfully treated by prompt first aid.

The hematogenous type, which is more disastrous, is caused by septic emboli lodging in the metaphysial region. In infants under 2 years, with thin cortex and more easily rupturable periosteum, less pressure is generated. In all cases the osteomyelitis behaves as an acute septic illness with localized tenderness.

Early diagnosis and early treatment are urgently important.

In infants supportive care and drainage of the abscess of the soft tissue when it occurs are wise, while in older children it is wise to drain earlier and only remove such bone as is needed for drainage. It is rarely necessary (as in adults) to make a window in the medullary canal. If the subperiosteal abscess is not drained promptly, it works along the bone until a large portion of it is killed.

Involvement of a joint, especially of the hip joint, is frequent. Early drainage and traction are important. Roentgen examination plays no part in the early diagnosis needed for the best results.

JANNEY, Wauwatosa, Wis.

DIAPHYSEAL ACLASIS. W. G. GILL, Proc. Roy. Soc. Med. **31**:11 (Nov.) 1937.

A girl of 11 years was admitted to the hospital, complaining of a lump on the arm, which had been noticed at the age of 5 years and which had slowly increased in size. It was not painful, but because it was causing inconvenience to movement at the shoulder joint the girl was taken to the hospital. The tumor was removed. The section showed it to be an exostosis consisting of cancellous bone. It had a cartilaginous tip. The child also showed many other features of diaphysial aclasis. Easily felt were exostoses of the fibulas, tibias and femurs and in the region of the knee joint. These signs were confirmed by roentgenograms, which showed clearly the widening of the metaphyses, the stippling and the abnormal trabeculation in the long bones. WILLIAMSON, New Orleans.

ACUTE RHEUMATIC ARTHRITIS WITHOUT CLINICAL EVIDENCE OF A LESION OF THE HEART. M. KAPLAN and J. PARROT, Gaz. d. hôp. **110**:1389 (Nov. 3) 1937.

A 19 year old boy, during his first attack of acute rheumatic fever, had bradycardia (pulse between 58 and 68) without other indications of involvement of the heart. Yet the electrocardiograms, taken repeatedly, showed that for one week there was complete dissociation of the auricles and ventricles and that the next week there was a great variability of the PR interval (between nine and eighteen hundredths of a second). The last observation is very rare. In the third week the electrocardiogram became normal. KAJDI, Baltimore.

SINUS PERICRANII. G. DIVIS, Časop. lék. česk. **75**:199 (March 6) 1936.

Divis reviews the literature on traumatic and congenital sinus pericranii and presents the case of a boy of 8 years with a pericranial sinus over the right frontal bone. The lesion measured 5 by 2 cm. and was about 2 cm. above the root of the nose. The diagnosis was verified by operation. The defect was corrected, with a good end result. STULIK, Chicago.

THE QUESTION OF CRANIOTABES. M. KASAHARA, K. KAWASHIMA and T. TOKUYAMA, Acta pædiat. **20**:95, 1937.

Rickets is not commonly encountered in Japan except in the maritime provinces which lie along the Sea of Japan. In Osaka, where this study was made, rickets is regarded as extremely rare: Only one or two typical cases are observed each year in the Osaka University Children's Clinic. Despite these facts, postnatal craniotabes is common among Japanese infants; it is observed with considerable frequency in well nourished breast-fed infants during the second and third months of life and becomes decreasingly common up to the sixth month. In the individual infant it disappears without any special therapeutic measures being taken. The abnormal elasticity is usually confined to the regions bounded by the lambdoid suture, the lateral fontanel and the small fontanel.

The authors took advantage of the clinical material supplied by the local infant health contests to investigate the incidence and origin of craniotabes in a systematic manner. In the examination of 3,908 infants aged from 1 to 9 months they encountered 316 with craniotabes (8.1 per cent).

Sixty-one per cent of the infants who exhibited craniotabes were males and 40 per cent were females. The incidence was highest during the third month of life (32.8 per cent) and decreased in the following order: fourth month, second month and first month. The average weight and average chest circumference of 316 infants with craniotabes were found to be somewhat above the corresponding average for healthy Japanese infants of the same age; the average total length and average head circumference of these patients approximated the normal averages. The extent of the abnormal elasticity varied from a barely palpable spot to an area 4 cm. in diameter; the patches of craniotabes were usually bilat-

erally symmetric. It was found more often in infants born in winter than in those born in summer. Most of the patients were full term infants; 99 per cent were breast fed. The mother's Wassermann reaction was known in 45 cases; in only 2 was it positive. None of the infants was conspicuously anemic. Of 72 infants who were submitted to more careful examination than the others, only 7 (9.7 per cent) showed a rachitic rosary and only 1 exhibited enlargement of the epiphyses.

The opinion is offered that postnatal craniotabes in young infants is not due to rickets. Further proof of the correctness of this assertion is supplied by a brief review of other reports from Japan and by a short description of the histologic features of craniotabetic skulls.

McCune, New York.

Multiple Joint Lesions with Symptoms of Still's Disease and with Unusual Roentgenologic Aspects. D. B. van Dorp-Beucker Andreae. Maandschr. v. kindergeneesk. **6**:467 (Sept.) 1937.

A boy of 6 years showed, together with pathologic changes in several joints of the extremities, many symptoms of Still's disease. Roentgenograms demonstrate strong osteoporosis of a large part of the skeleton and changes in several epiphyses resembling aseptic necrosis. Many therapeutic measures resulted in an important amelioration of the physical and psychic condition of the boy.

van Creveld, Amsterdam, Netherlands.

Diseases of the Eye

Hereditary Paralysis of the Abducens Nerve. R. C. Laughlin, Am. J. Ophth. **20**:396 (April) 1937.

Laughlin reports a case of hereditary paralysis of the left external rectus muscle in a child whose mother exhibited a typical Duane syndrome. He briefly reviews the literature and gives the following summary:

"A case of hereditary paralysis of the abducens nerve is presented, in which five members in three generations of the same family were afflicted; two were examined. Ten other cases are reported from the literature. A statistical analysis of the data shows that in this condition a majority of females and of left eyes are affected."

W. S. Reese. [Arch. Ophth.]

Visual Impairment Due to Neglect. Frank E. Burch, Minnesota Med. **20**: 646 (Oct.) 1937.

In a study of the causes of blindness taken from the records from the Minnesota State School for the Blind and from the register of sight-saving classes in St. Paul, Minneapolis and Duluth and also from other available private and public sources, the author finds that hereditary and inherited anomalies constitute practically one fourth of all causes of actual blindness. In the juvenile group admitted to the school for the blind the percentage is even higher, being 38 per cent. The author emphasizes the importance of private and public discussion relative to prevention of blindness through birth control. Fifteen per cent of the children admitted to the school for the blind were blind because of transmitted syphilis. The value of the nationwide campaign to avoid syphilis is discussed. In 12 per cent of cases blindness is caused by accidents, either industrial or connected with sports. The widespread use of nonshatterable lenses is advocated by the author. The importance of the removal of eye strain and fatigue is emphasized, as well as the value of proper illumination. The author urges that physicians in all branches of medicine should recognize the importance of competent periodic examinations of the eyes.

Anderson, Minneapolis.

CONJUNCTIVAL PEMPHIGUS. M. H. WHITING, Brit. J. Ophth. **21**:529 (Oct.) 1937.

The case is of interest because of the beneficial effect of the wearing of a contact glass filled with liquid paraffin. In the right eye this was possible without operative intervention, but in the left eye a lower fornix was first made with a mucous membrane graft from the lip. In the right eye vision improved from ability to count fingers at 1 meter to 6/24 or better, and in the left eye, from perception of movements of the hand to 6/60, in three months.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

CONTRIBUTION TO THE STUDY OF INFANTILE GLAUCOMA. BENITO JUST TISCORNIA, Rev. méd. latino-am. **22**:1329 (Sept.) 1937.

Infantile glaucoma, also called hydrophthalmos and buphthalmos, is an ocular dystrophy characterized clinically by distention of the globe accompanied by hypertension. It results from an alteration in the intraocular fluid. The early manifestations in a few cases appear shortly after birth; the condition is bilateral, but on occasion may affect only one eye. Most authorities make a distinction between infantile and juvenile glaucoma. The latter appears in the second or third decade and has a decided hereditary tendency. Other authors contend that it is impossible to distinguish between glaucoma of the middle-aged and glaucoma of the senile.

Consanguinity of the parents, hereditary syphilis and congenital malformation are the most common causes. The author saw 156 blind children, 13, or 8.9 per cent, with glaucoma. Of the 13 cases, the condition in 8 was due to consanguinity and in 6 to syphilis. A bibliography of 127 references is appended.

DWYER, Kansas City, Mo.

RARE FORMS OF TAPETORETINAL DEGENERATION: REPORT OF CASES. K. LISCH, Klin. Monatsbl. f. Augenh. **98**:498 (April) 1937.

Lisch observed an unusual form of tapetoretinal degeneration in 4 boys of a family of 6 children. One boy aged 13 and a girl aged 17 had healthy eyes.

Consanguinity of the parents did not exist, and ocular disorders in other members of the family were unknown, except in a sister of the children's father; she could not see well with one eye and had a cataract extracted. The ages of the 4 boys were 20, 19, 16 and 15, respectively. Vision was reduced in each of them, but it did not deteriorate allegedly except in the boy aged 19, who had bilateral holes in the macula. The peripheral field of vision was not considerably narrowed in any of them, and in 2 it was normal. Two boys had defects in the nasal and upper portions of the field, coupled with central scotomas and with reduced dark adaptation.

The changes in the maculas of these 4 boys consisted of irregular pigmentation and radial streaks, which may represent folds in the internal limiting membrane, produced by edema. The degenerative changes consisted of grayish white retinal foci of varying form and size and of fine irregular accumulations of pigment. Three boys had atrophy of the optic disks, which were not well outlined. The central retinal vessels showed invagination resembling perivasculitis. This symptom was considered indicative of marked pathologic involvement of the vascular system of the retina. The boys were intellectually normal, with the exception of the boy aged 19, who had choreatic restlessness and was physically underdeveloped.

K. L. STOLL. [ARCH. OPHTH.]

INTRASCLERAL EPITHELIAL CYST. M. SALZMANN, Ztschr. f. Augenh. **92**:275 (Aug.) 1937.

Five cases of this rather unusual condition are reported, with detailed histologic studies in 3. One cyst was successfully removed by simply dissecting away

the outer wall, the epithelium of the inner wall being allowed to take the place of the normal conjunctiva. In all the cases the cysts followed perforating injury to the region of the limbus corneae by blunt instruments and were associated with prolapse of the iris and gaping wounds during healing. In 4 of the 5 cases the condition occurred in children from 4 to 12 years of age. The cysts appeared some years after the original injury, and growth was accelerated later in the course of the disease. Such a cyst is characteristically bean shaped, kidney shaped or even sausage shaped, with the largest circumference away from the limbus.

The largest tumor in Salzmann's cases extended as far back as the insertion of the inferior rectus muscle, but others have reported cysts in shrunken globes which have extended as far back as the optic nerve. There was no invasion of the cornea in this case, except where it was badly damaged by the original injury.

The cysts were scleral white and covered with normal movable conjunctiva. The latter factor alone differentiates this type of cyst from scleral ectasia and intercalary staphyloma. The edges of the cysts were sharply demarcated from the normal sclera. The cysts were translucent and had no spots or streaks of pigment. Histologically, they were found to be lined with several layers of pavement epithelium. The basal layer was more similar to corneal than to conjunctival epithelium. Salzmann feels that this layer originates from the cells in the region of the limbus, which proliferates as it would in healing over a flat surface. The walls of these cysts were made up principally of normal scleral connective tissue, as if the cysts had merely dissected in between the layers of the sclera. The occurrence in children and the limitation of the cysts to the anterior sclera where the lamination was more definite would uphold this idea. The cysts were filled with a clear fluid, which was felt to be a secretion product of the epithelium and not aqueous. In 2 cases part of the cyst was intraocular. In 1 case the cyst invaded the posterior chamber, and there was a free communication with the intrascleral cyst. In the other case the cyst occurred in the anterior chamber, but no direct communication was found with the intrascleral cyst. The relation to epithelial cysts in the anterior chamber is obvious and is discussed at length. Drawings and photomicrographs illustrate the article.

H. Gifford Jr. [Arch. Ophth.]

Ring Sarcoma of the Iris and Ciliary Body: Report of a Case. Von Ove Boje, Acta ophth. **15**:239, 1937.

The case reported is notable first for the age of the patient, a 6 month old boy, and second for the extreme rapidity of the growth of the tumor, only three weeks having elapsed between the first appearance of a small brownish yellow spot on the iris and the extension of this pigmented area over the entire iris. The diagnosis made prior to enucleation was confirmed by microscopic examination.

O. P. Perkins. [Arch. Ophth.]

Skin Diseases; Allergy

Telangiectasis Maculares Eruptiva Perstans: Report of an Early Stage in a Child. Franklin I. Ball, Arch. Dermat. & Syph. **36**:65 (July) 1937.

A case in which eruptive telangiectatic macules occurred in a girl aged 10 is reported. The child was moderately obese, following the tendency of most of the patients. The disease usually occurs in obese women. The obesity is considered by most authors to be an indication pointing to endocrine causes. The relationship to urticaria pigmentosa is discussed and is attributed to the large number of mast cells which occur in the sections from patients with both diseases. This case appeared to be of special interest because there was spontaneous disappearance of the lesions.

Dulin, Iowa City.

SPECIFIC TREATMENT OF STAPHYLOCOCCIC INFECTIONS OF THE SKIN. PAUL F. STOOKEY and LOUIS A. SCARPELLINO, Arch. Dermat. & Syph. **36**:106 (July) 1937.

The authors report 6 cases of staphylococcic infection of the skin with necrotizing ulcers. The infections were treated with staphylococcus antitoxin. In 3 cases unquestionable benefit was derived from the therapy. In the authors' opinion the "use of the staphylococcus antitoxin is justified in cases of staphylococcic septicemia and of necrotizing ulcers due to pigment-producing toxigenic staphylococci."

DULIN, Iowa City.

KERATOMA PALMARE ET PLANTARE HEREDITARIUM, WITH SPECIAL REFFERENCE TO ITS MODE OF INHERITANCE AS TRACED IN SIX AND SEVEN GENERATIONS, RESPECTIVELY, IN TWO CHINESE FAMILIES. HUEI-LAN CHUNG, Arch. Dermat. & Syph. **36**:303 (Aug.) 1937.

By definition keratoma palmare et plantare hereditarium is a congenital symmetric thickening of the horny layer of the epidermis of the palms and soles. The disease appears at birth or soon after and is not associated with inflammatory symptoms. The histologic picture consists of hypertrophy of the stratum corneum. The prickle cells and granular layers are normal. The condition is singularly resistant to treatment, but some relief is obtained by the use of ointments containing salicylic acid, which keep the skin more flexible and reduce the horny layer. The thickening recurs when the treatment is discontinued.

In the two Chinese families observed, there occurred in the Yang family, in seven generations, 24 affected offspring and 25 nonaffected offspring. In the Wang family, in six generations, there were 28 offspring affected and 30 nonaffected. From the genealogic charts the following inferences were drawn: The trait does not skip a generation. The trait appears in a relatively large number of members of the same family. Only persons who show the trait transmit the disease. Normal offspring of an affected parent never transmit the condition. For each generation the number of affected offspring to a parent tends to be about the same as the number of normal offspring, provided that the number of children is large.

The analysis shows that the trait is a single dominant characteristic.

DULIN, Iowa City.

BULLOUS PEMPHIGUS TREATED BY RUBIAZOL: REPORT OF TWO CASES. CLELIA and EMIL HURMUZACHE, Bull. Soc. de pédiat. de Iasi **7**:101 (Oct.-Dec.) 1936.

The authors relate observations on 2 cases of bullous pemphigus in infants with severe constitutional manifestations, in which rapid improvement was obtained in forty-eight hours by the use of rubiazol (the hydrochloride of 4-sulfamido-2′: 4′-diaminoazobenzene).

LESLIE, Evanston, Ill.

ACRODYNIA IN CHILDREN IN THE REGION OF TOULOUSE. M. BÉZY, Bull. Soc. de pédiat. de Paris **35**:63 (Jan.) 1937.

Acrodynia is becoming more and more common in the region of Toulouse in France. It appears in localized epidemics, the greater incidence occurring in cities. It is more frequently encountered among girls than among boys, particularly in the second year of life. The majority of cases are observed in spring, and there would appear to be some connection with the illnesses most common at that season. Occasionally direct contagion can be traced from one patient to another, but on the whole the mode of transmission remains obscure. Practically all patients recover.

BENJAMIN, Montreal, Canada.

FREQUENCY OF BENIGN CALCIFIED EPITHELIOMA OF THE SKIN IN CHILDREN. MARCEL FÈVRE, Bull. Soc. de pédiat. de Paris **35**:94 (Feb.) 1937.

Six cases in which this condition occurred in children, observed since 1927, are reported. All the patients were successfully operated on. The tumor is hard and adherent to the overlying skin but is movable at its base. Roentgenographic examination usually shows some calcification. Frequently small calcareous masses are extruded from openings through the skin. A total of 44 cases was observed; the lesion in 27 was located about the face and neck. Histologically the tumor consists of a mass of epithelial cells with calcification in spots and a connective tissue stroma; there are never any abnormal cells showing karyokinesis or metastases. When the tumor is properly excised there is no recurrence. Such a tumor is considered an embryonic ectodermal inclusion tucked away more or less deeply under the skin.

BENJAMIN, Montreal, Canada.

ALOPECIA IN A CHILD WITH A LONG NECK WITH EIGHT CERVICAL VERTEBRAE. H. JANET and E. WOLINETZ, Bull. Soc. de pédiat. de Paris **35**:235 (April) 1937.

A boy aged 6 years had had patchy baldness from the age of 4 years. Hair grew in but fell out again. The eyebrows were bare of hair, and the body and extremities lacked lanugo. The nails showed striations and pitting. The boy had had numerous infections. His neck was unusually long and contained eight cervical vertebrae. The possibility of irritation of the sympathetic nerves is discussed, but in the absence of the usual manifestations associated with this condition this explanation seems hardly tenable.

BENJAMIN, Montreal, Canada.

TELANGIECTASIS OF OSLER. BRAULIO XAVIER FILHO, JOSE SOBRINHO and URBANO FREITAS, J. de pediat., Rio de Janiero **4**:448 (Oct.) 1937.

The boy described was 2 years old, and the tumor was on the palm of the right hand. It was associated with an essential thrombocytopenia of Frank. The number of platelets was increased and some relief of symptoms from the tumor was obtained by therapy with vitamin C.

SANFORD, Chicago.

A SOURCE OF INFECTION FOR MOLLUSCUM CONTAGIOSUM? GÖRL, München. med. Wchnschr. **83**:1589 (Sept. 25) 1936.

The contagiousness of molluscum contagiosum has been recognized for a long time. The disease is due to a filtrable virus, and the period between inoculation and the formation of a nodule is about three months. The long period of incubation makes it difficult to determine the source of infection. Görl cites 3 cases in which he feels that contact with wool was the means of infection.

BRAHDY, Mount Vernon, N.Y.

ICHTHYOSIS AND ICHTHYOSIS-LIKE DISEASES: II. REPORT OF A CASE OF ERYTHRODERMA CONGENITALE ICHTHYOSIFORME (BROCQ). Y. KURIHARA, Acta dermat. **27**:108 (Dec.) 1936.

The author describes a typical case of erythroderma congenitale ichthyosiforme (Brocq), the patient being a 10 year old boy who had symptoms resembling the Adams-Stokes complex, such as bradycardia, paroxysmal paleness of the face, a feeling of illness when mentally excited and periods of stuttering. According to the author, the erythema in this disease is mostly labile and indistinct and is not an important symptom, and the clinical picture does not differ essentially from that of ichthyosis congenita. Erythroderma congenitale ichthyosiforme is a certain form of ichthyosis congenita characterized by erythema. The author does not agree with those investigators who maintain that keratoma palmare et plantare hereditarium or naevus keratoticus are localized forms of erythroderma congenitale ichthyosiforme (Brocq).

BLOOM, New York. [ARCH. DERMAT. & SYPH.]

FORMES FRUSTES OF ACRODYNIA. T. HALBERTSMA, Maandschr. v. kindergeneesk. **7**:14 (Oct.) 1937.

Besides the ordinary, classic cases of acrodynia, there occasionally occur formes frustes, in which diagnosis is extremely difficult. The symptom of tachycardia is in these cases a factor of especial pathognomonic significance. The author gives a description of 4 patients in all of whom the syndrome was incomplete and in whom redness of the hands and feet was lacking. The first patient, a girl aged 2½ years, suffered principally from psychic changes and pains; the second, a girl aged 1 year, showed photophobia; the third, since the age of 2 months had had predominantly cutaneous symptoms; and the last patient, a girl aged 13 months, showed alarming restlessness and was always crying, especially during the night.

VAN CREVELD, Amsterdam, Netherlands.

Surgery and Orthopedics

EXTENSIVE BURNS; TREATMENT WITH SILVER NITRATE AND METHYL ROSANILINE. H. E. BRANCH, Arch. Surg. **35**:478 (Sept.) 1937.

After giving a brief résumé of modern methods of treating burns, Branch describes a new method in which a 1 per cent aqueous solution of methyl rosaniline is used for a spray and a 10 per cent solution of silver nitrate for swabbing the burned areas. It was found that the 10 per cent solution of silver nitrate acts on the proteins of the serum exuding from the burned area to lay down immediately a milky white coagulation. This coagulum the methyl rosaniline stains violet. The dye also aids in destroying bacteria, thus preventing infection. This method, the author maintains, upholds the principles set up for the treatment of burns with tannic acid but has several advantages: It reduces shock and pain, the incidence of toxemia and the likelihood of infection.

KAISER, Rochester, N. Y.

CLEFT PALATE: A CORRELATION OF ANATOMIC AND FUNCTIONAL RESULTS FOLLOWING OPERATION. W. RITCHIE, Arch. Surg. **35**:548 (Sept.) 1937.

The report concerns 100 cases of cleft palate in which an operation was done for repair. The anatomic results were carefully tabulated, and the phonetic results were noted. In the phonetic tests particular stress was placed on disturbances in the quality of tone and in the articulation. The purpose of the study was to correlate the speech defects with the anatomic results. It was found that good anatomic results do not necessarily mean good functional results. In the cases presented the ultimate speech in 42 per cent was classed as excellent, in 43 per cent as good, in 14 per cent as fair and in 1 per cent as bad or unintelligible.

KAISER, Rochester, N. Y.

SPINAL ANESTHESIA: SUBARACHNOID INJECTION OF PROCAINE. W. H. LIVERMORE, M. Rec. **146**:334 (Oct. 20) 1937.

This method of obtaining anesthesia is urged by Livermore, who describes the preoperative preparations, technic and dosage. The drop in blood pressure caused by the dilatation in the splanchnic area is discussed, and the lowered position of the head and upper part of the body to permit proper circulation by gravity is emphasized.

WESTON JR., Columbia, S. C.

INSULATING PATCHES AND ABSORBABLE SUTURES MADE FROM FETAL MEMBRANES. H. L. JOHNSON, New England J. Med. **216**:978 (June 3) 1937.

Disruption of wounds from infection or too early digestion of catgut, with formation of excessive amounts of serous exudate, seems to be the chief factor

giving rise to the demand for an improved absorbable suture. Fetal membranes properly prepared, it is believed, will greatly alleviate most of the aforementioned difficulties, as shown by a series of studies in experimental animals.

The idea of protecting certain locations of the body from the formation of crippling postoperative adhesions is not new. In the use of properly prepared and preserved membranous patches made from human amniotic and bovine allantoic and amniotic membranes, it is believed that a substantial contribution has been made to the successful handling of this difficulty.

A careful operative technic in the application of the patch is essential. Gross and microscopic study of the tissues involved shows that this new technic is safe and effective in the experimental animal. The use of insulating patches may prove especially applicable in surgical operations on the peritoneal cavity, tendons, nerve, blood vessels and joints.

GENGENBACH, Denver.

DEFORMITIES OF THE VERTEBRAL COLUMN: THEIR CORRECTION AND CARE AND THEIR RELATION TO THE INTERVERTEBRAL DISKS. E. L. COMPERE and D. C. KEYES, Cir. ortop. y traumatol., Habana **4**:237 (Oct.-Dec.) 1936.

The intervertebral disks are prominently concerned in maintaining the normal function of the vertebral column. Lesions of the vertebral disks or of the vertebral bodies themselves or of both, caused by disease or trauma, are generally followed by deformity of the spine.

In correcting spinal curvatures one must bear in mind this function of the intervertebral disks. If some of the disks have become thinned through loss in the pulpous nuclei or through displacement of these nuclear elements, the ensuing spinal deformity cannot be corrected adequately without internal fixation by means of some type of spinal fusion. The authors describe typical spinal deformities, including scoliosis, kyphosis due to spinal tuberculosis, compression fractures of vertebral bodies and round backs, produced by lesions of the vertebral disks. In most of the patients an improvement of position was obtained by the use of a plaster cast that included the trunk and legs and had extenders and hinges at the level of the most bulging point of the deformity. In patients with old, advanced lesions correction was maintained by producing fusion of the spinal column by excision of the articular surfaces, fracture of the spinous processes and use of tibial bone grafts.

HERRON, Monroe, La.

CLUBFOOT. R. PENALVER, Cir. ortop. y traumatol., Habana **4**:275 (Oct.-Dec.) 1936.

Penalver reviews different varieties of clubfoot. He presents in detail a case of the equinovarus variety and differentiates this from the congenital and acquired varieties. Treatment consisted in tenotomies and fasciotomies, followed by immobilization and later by astragalectomy in the right foot and cuneiform external tarsectomy in the left foot.

HERRON, Monroe, La.

TREATMENT OF SCOLIOSIS. A. INCLAN, Cir. ortop. y traumatol., Habana **5**:67 (April-June) 1937.

Inclan relates the difficulties encountered in his country in the treatment of scoliosis. There is first the delay in diagnosing the condition and then the erroneous prognosis of its benignity, the climate and the difficulty of managing young patients. This paper is written for the general practitioner rather than for the orthopedic surgeon.

Postural scoliosis is benign and easily treated, but structural scoliosis is serious. One must find the causes of the structural changes in the vertebrae, whether congenital, idiopathic, dynamic or pathologic.

Roentgenograms should be taken regularly. Inclan states that for twenty-five years he has fought against a local obstacle: the impossibility of using irremovable

apparatus, on account of the tropical heat. On the other hand, many failures have been encountered with removable apparatus. Gymnastics alone do not correct structural scoliosis or impede its progress, and the young patients will not give up their accustomed entertainments, so that an early surgical procedure is necessary. Yet only 2 of 302 private patients have submitted to early operation.

HERRON, Monroe, La.

Miscellaneous

THE CHEMISTRY OF URINE IN THE DIAGNOSIS OF EMBRYONAL TUMORS. S. E. OWEN, Q. G. POLANCO and L. H. PRINCE, Am. J. Cancer **31**:613, 1937.

A qualitative chemical test for the urinary gonadotropic substances is presented. Of 44 cases of teratoma testis in which assays for the urinary gonadotropic substances were positive, the chemical test was positive in 39. Of 26 instances in which gonadotropic substances amounted to 400 or more mouse units per liter, the chemical test was positive in 25. The chemical test was positive in all the 11 urines of pregnant women examined as controls. By the preparation of special extracts of urine, many substances which interfere with the test are eliminated, and the reacting endocrine substances are concentrated. It is believed that the test presented is suitable as a qualitative diagnostic aid in cases of teratoma testis.

FROM AUTHORS' SUMMARY. [ARCH. PATH.]

IODINE IN DISORDERS OF INFANCY. E. TRAVELLA, Rev. Soc. de pediat. de Rosario **2**:134 (Sept.) 1937.

Iodine is indicated in adjunct therapy for syphilis, rheumatism, malaria and other debilitating conditions.

SANFORD, Chicago.

SILVER IMPREGNATION OF ERYTHROCYTES IN LEAD POISONING IN INFANTS. M. KASAHARA and M. NAGAHAMA, Folia haemat. **56**:221, 1936.

Tables showing the blood counts and the counts of 10,000 erythrocytes impregnated with silver according to the described technic in 33 cases of lead poisoning in infants, as well as similar tables in cases of various types of secondary anemia, are given. In lead poisoning there is a high percentage of cells which take the silver impregnation showing a webbed, threadlike or granular form similar to the types seen in reticulocyte stains. The incidence of the granular form, which is the most common, parallels the occurrence of basophilic stippling. Normal red cells show only a finely granular form in contrast to the coarsely granular, weblike and threadlike forms seen in plumbism and other anemias.

HEERSMA, Chicago.

MORPHINE SUSCEPTIBILITY IN INFANCY. U. GRÜNINGER, Monatschr. f. Kinderh. **71**:180 (Oct.) 1937.

On the basis of his observations on children undergoing operation, Grüninger concludes that the average infant can tolerate more than one drop of the ordinary tincture of opium, i. e., from 0.22 to 0.35 mg. of morphine.

GERSTLEY, Chicago.

CHANGES IN POPULATION IN AUSTRIA. E. FÜRTH, München. med. Wchnschr. **84**:380 (March 5) 1937.

During the years from 1926 to 1935, inclusive, 816,130 legitimate births were recorded in Austria. During the same period there were 478,590 marriages. In 1935 the death rate for the total population (13.65) exceeded the birth rate (13.47) for the first time.

BRAHDY, Mt. Vernon, N. Y.

WARNING AGAINST THE USE OF COUGH SYRUPS IN YOUNG INFANTS. P. FRICK. München. med. Wchnschr. **84**:487 (March 26) 1937.

Four infants under 5 months of age were admitted to the hospital because of diarrhea and vomiting. One infant died of acute intestinal intoxication. The illness of each one followed the administration of a cough syrup. Because the expectorant effect of cough syrups is questionable, the author sees no reason for prescribing them for young infants.

BRAHDY, Mt. Vernon, N. Y.

NICOTINE INTOXICATION IN A CHILD. S. RUDBERG, Svenska läk.-tidning. **34**:929 (June 25) 1937.

A boy of 1½ years fell ill after having tasted an aqueous solution containing nicotine in 10 per cent concentration, used for spraying plants against parasites. He immediately began to vomit, rapidly grew worse and eventually collapsed. After treatment with gastric lavage and stimulants, he recovered and was discharged free from symptoms on the third day. The stools, urine, blood picture and sedimentation rate were normal.

WALLGREN, Göteborg, Sweden.

Society Transactions

AMERICAN PEDIATRIC SOCIETY AND SOCIETY FOR PEDIATRIC RESEARCH

Joint Meeting, Great Barrington, Mass., May 5-7, 1938

KENNETH D. BLACKFAN, M.D., *President*

HUGH MCCULLOCH, M.D., *Secretary*

(Concluded from page 459)

Third Session

Friday Morning, May 6

FAMILIAL PROGERIA. DR. HAROLD L. HIGGINS, Boston.

Dr. Talbot (*Monatschr. f. Kinderh.* **25**:643, 1923) described a girl of 12 years who had the appearance of a woman of 40 as a patient with atypical progeria. In 1934, at the age of 26, this patient died of pneumonia; she had had 4 children, 3 of them normal and 1 an almost exact replica of his mother. I am now able to report 3 cases of premature senility which appeared in this family in grandmother, mother and son, covering 3 generations.

The main characteristic of these patients was congenital and progressing looseness of the skin, especially of the face, the chest, the abdomen and the genitalia. Each as a child had the appearance and the voice of an old person. Hypertension (blood pressure 183 systolic and 152 diastolic) was present at the age of 12 years in the mother, and asthma and a tendency to pneumonia were noted in both the grandmother and the mother. Growth, the composition of the blood chemistry and sexual maturity were essentially normal.

These patients might be said to have progeria, in that they appeared old while still young. But their clinical picture was not that of Gilford's progeria in that they were not dwarfed, emaciated, bald or sexually undeveloped.

The pathologic alteration of the skin appeared clinically to be in the corium (mesodermal). Good texture, moistness, and healthy hair indicated normal cutaneous epithelium. The elastic tissue of the skin seemed functionally at fault, and probably the elastic tissue of the larynx, arteries and lungs was also imperfect.

Other familial diseases of the corium and of the elastic tissue include epidermolysis bullosa, Recklinghausen's disease (?) and india rubber skin (cutis laxa). Cutis laxa has been shown to have existed as a dominant hereditary characteristic in one family in Germany. In the family of the present study the cutaneous condition was a recessive factor, although familial webbed toes were present as a dominant factor.

DISCUSSION

DR. FRITZ TALBOT, Boston: This group of cases is interesting because here again is an example of what increased knowledge is doing for medical practice. Dr. Higgins has performed the important function of differentiating two types of condition that in the past were generalized and called progeria. The future will tell more in detail what these two conditions are and what they mean.

I might draw attention to the fact that Charles Dickens was a keen endocrinologist. All are familiar with the fat boy and with Dickens' conscientious description of that particular type, and some are also familiar with his accurate

description of the giant. Dr. Higgins' description made me think that there are certain similarities between the acromegalic giant, particularly the pituitary type, and a patient with this condition. The acromegalic giant grows rapidly and is strong early in life, when he is a good person for the circus; but he becomes weak prematurely and dies relatively young.

DR. CHARLES G. KERLEY, New York: I hope Dr. Higgins will tell us something about the duration of growth in cases of progeria and about the relation between chronologic age and osseous age during the period of development.

In these cases does the condition bear any relation to the osseous retardation associated with cretinism and other subthyroid states?

DR. HAROLD L. HIGGINS, Boston: The patients that I described showed no retardation in osseous age. Patients with Gilford's progeria, however, never reach maturity, and they do not procreate; they would compare with the pituitary dwarfs, who also never procreate.

It is interesting that in this family the familial disease affected 3 members of 11 who were possible patients. Apparently it is a recessive characteristic. In this same family webbed toes, which appeared in 5 of 8 members, were a dominant characteristic.

RICKETS IN MONKEYS (MACACUS RHESUS). DR. HENRY J. GERSTENBERGER, Cleveland.

This report presents parts of a comprehensive study of rickets in monkeys (Macacus rhesus). The monkeys belonged to three groups, numbering respectively 21, 27 and 33 animals. The first group received a diet with a calcium-phosphorus ratio of 0.49. Of the second group, 21 monkeys were fed a similar diet and the remainder, 6 monkeys, were on admission given a diet with a higher calcium-phosphorus ratio, namely, 1.3. The 21 monkeys of the second group which on admission received the diet with a calcium-phosphorus ratio of 0.49 were later given the diet containing the higher ratio. All of the members of group 3, 33 monkeys, 31 of which are still alive, received the diet with the calcium-phosphorus ratio of 1.3.

It is estimated that each monkey ingested in both diets 2.56 Gm. of phosphorus per week; in the lower calcium diet, 1.26 Gm. of calcium per week, and in the higher calcium diet, 3.08 Gm. of calcium per week.

In all of the monkeys but 1, after an interval varying from three to ten months there developed rickets which was characterized in the blood serum by an essentially normal calcium level and a decidedly abnormal, low phosphorus level; in other words, the monkeys whose exposure to actinic rays was prevented acquired the type of rickets most frequently encountered in the full term human infant.

The rachitic monkeys were used in various studies planned to elucidate, if possible, the pathogenesis of the rickets and rachitic spasmophilia seen in human infants. Following are some of the results obtained in addition to those just presented.

1. The low phosphorus, high calcium type of rickets healed readily when the face of the animal was exposed to half of an erythema dose of ultraviolet radiation six times per week. It was also established that cod liver oil and viosterol brought about healing.

2. The healing produced as described under paragraph 1 was accompanied by the appearance of spasmophilic signs in 5 of 8 monkeys fed the low calcium diet; none of those fed the high calcium diet reacted in this manner.

3. Parenteral administration of solutions containing phosphates or phosphoric acid brought about complete healing, as registered in the roentgenogram. This healing was accompanied by changes in the level of calcium and of phosphorus in the blood serum, which usually culminated in normal values for both. Phosphates of potassium, sodium, ammonium, calcium, rubidium and lithium were used; of these, the last named had the slowest and also the most peculiar action.

The animals treated with calcium phosphate healed no better than did those given injections of the phosphate solutions of potassium, sodium and rubidium. Injections of calcium in the form of calcium lactate and a lactic acid in the form of potassium lactate and calcium lactate had no effect. The most rapid results were obtained with solutions of glycerophosphoric acid and orthophosphoric acid. It is suggested, therefore, that the term phosphatization rather than calcification might better be used in connection with the healing process of this form of rickets.

4. Injection of thyroxin brought about healing changes in the rachitic metaphysis. These were accompanied by loss in weight, which occurred even though the dose used at first was decidedly reduced in the latest tests. It is considered probable that the effect of thyroxin, at least when it was given in the smallest doses, was due not to liberation of phosphates as a result of an assumed increase in metabolism and destruction of tissue but rather to alteration in the mineral and water balance of the animal. Injections of parathyroid extract and extract of the anterior lobe of the pituitary gland when given alone had no demonstrable healing effect.

5. Roentgenograms made at frequent and regular intervals revealed that the rickets observed in the monkeys passed through a stage in which healing-like changes occurred in the part of the metaphysis adjoining the diaphysis. These changes came from the diaphysis and proceeded toward the epiphysis. Gradually the characteristic goblet-shaped rachitic bone appeared at the distal end of the ulna. Consequently it is concluded, particularly because there was no indication of progressive healing in the blood serum, that what has been seen is a part of the normal development of rickets in monkeys.

6. In some of the monkeys receiving sodium and potassium glycerophosphates the injections were continued after complete healing had occurred; it was found that, notwithstanding, rickets had developed for the second time. This finding seems to indicate that while these solutions were able to bring about phosphatization of the original rachitic metaphysis, they could not prevent the recurrence of the rickets even though they were being continuously administered, apparently because of the absence of a controlling influence which sunlight evidently is able to exert. It may even be that their continued administration in the doses used was partly responsible both for the failure of the healing process to progress to the stage of permanently normal bone and for the second appearance of the rachitic metaphysis.

DISCUSSION

DR. DANIEL C. DARROW, New Haven, Conn.: What was the approximate age of the monkeys when they were first given the diet?

DR. BENGT HAMILTON, Chicago: Dr. Gerstenberger has a wonderful method of studying rickets; the condition in monkeys is like that in human beings, and I wonder if the tendency to spontaneous healing that one sees in human beings is also present in these animals.

DR. HENRY J. GERSTENBERGER, Cleveland: The ages of the monkeys varied, I should judge, from 6 months to 2 years.

Spontaneous healing of the rickets of monkeys does not occur, according to my experience, and I have never seen it occur in human beings. The so-called spontaneous healing which one sees in human infants is due to an unknown or unappreciated exposure of the particular rachitic infant to sunlight; this healing is observed most often in the spring.

My associates and I gave 81 monkeys the diet I described, and in every one rickets developed. I am inclined to think that with rickets there exists a lack of control of the mineral and water metabolism and that this operates through the vegetative and the endocrine system and plays an important role in the production of the disorder.

DR. FRANK C. NEFF, Kansas City, Kan.: May I ask the importance of rickets in the zoo, where all sorts of conditions develop in monkeys.

DR. HENRY J. GERSTENBERGER, Cleveland: I cannot answer that well because I have not followed the animals in the zoo. I am sure, however, that if a monkey is allowed to be outside in the sunlight it will not have rickets. I might add that 0.6 cc. of cod liver oil healed rickets of 1 of our monkeys.

TWO CASES OF MULTIPLE DEFICIENCY DISEASE RESEMBLING BERIBERI AND SPRUE. DR. WARREN R. SISSON, DR. JOHN P. HUBBARD (by invitation) and STEWART H. CLIFFORD (by invitation), Boston.

Two cases in which unusual clinical findings suggested a primary nutritional disturbance are presented. The children lived under excellent hygienic conditions, and it seems likely that in each case perversions of appetite arose which may well have caused definite lack of important accessory foods and disturbances in absorption. The 2 cases, although presenting different findings, suggested a primary deficiency disease.

CASE 1.—B. S., a 9½ year old girl in early adolescence, was brought up in affluence and was under careful medical supervision from birth. She presented changes in personality, disturbance in gait, general edema, marked cutaneous lesions of the face and extremities, tachycardia, paresthesia and marked pain in the muscles and joints. A typical steppage gait developed with marked talipes equinus. The symptoms disappeared after administration of a diet with a high vitamin content and yeast. After this bronchopneumonia developed and the patient died three days later. The autopsy showed degeneration of nerve fibers. Laboratory studies showed no disturbance in the chemical composition of the blood and no evidence of any infection except the terminal one.

CASE 2.—K. R., a 12 year old girl who was under observation for one year, was subjected to extensive study because of chronic diarrhea and edema associated with unusually low levels of serum protein and serum calcium. The onset was associated with anorexia, nausea and vomiting, resulting apparently from continuous anxiety and nervous tension at school. There followed a general deficiency in diet, progressive loss of weight and successive development of edema, tetany, diarrhea, purpura, peripheral neuritis and paresthesia. No specific dietary deficiency could be determined as the primary underlying difficulty. Clinical improvement followed parenteral liver therapy. Relapses occurred twice after discontinuance of this treatment. The value of the serum calcium returned to normal after therapy, but the serum protein, although improved, remained at remarkably low levels. Large doses of vitamin D also appeared beneficial. The terminal relapse occurred in association with an infection of the respiratory tract. The patient finally failed to respond to parenteral administration of liver. Intramuscular injections of nicotinic acid were without benefit. Death finally resulted, following an intracranial hemorrhage. Postmortem examination failed to reveal the primary cause of death.

DISCUSSION

DR. DANIEL C. DARROW, New Haven, Conn.: Did you do any determinations of fat in the stools in the second case?

DR. A. A. WEECH, New York: An outstanding characteristic of many nutritional diseases in man is their tendency to occur in multiple form. In China my associates and I saw many children whose diets consisted almost exclusively of the cereal grains. Such diets are low in protein and fat, in calcium and phosphorus, in vitamins A and D and at times in the vitamin B complex. The children, like those described by Dr. Sisson, frequently exhibit signs of multiple deficiency disease. Because the dietary fault is multiple it is often impossible to know the important factor behind many of the symptoms. In particular I am interested in knowing whether there is any real relation between deficiency of the vitamin B complex and edema due to a low level of serum proteins. Such a relation has been reported. In cases of the type described

much knowledge could be gained from serial measurements of the serum protein content along with records of the actual food intake. Vitamin B_1 improves the appetite and conceivably exerts an effect on the amount of serum proteins only by promoting the ingestion of more protein.

DR. WILBURT C. DAVISON, Durham, N. C.: Deficiency diseases apparently occur in Boston as well as in North Carolina and Virginia. The first autopsy in a case of pellagra was reported from Massachusetts. The presence of pellagra can be demonstrated by the accentuation of the symptoms and signs, e. g., dermatitis, soreness of the tongue and diarrhea, after exposure to sunlight for an hour on three successive days. The clinical manifestations of many pellagrins may disappear in the hospital if the patients are kept away from the sunlight, even though the diet is unchanged. The urine also can be tested for a porphyrin-like substance.

DR. WARREN R. SISSON, Boston: As to the fat content of the stools, we found that there was definite steatorrhea in the second case; 36 per cent of the twenty-four hour specimen of dried feces was fat. It was impossible to associate this steatorrhea with any pancreatic lesions. Microscopic studies indicated that the pancreas was normal.

From our experience, especially in the second case, we feel that prolonged parenteral administration of liver is the most essential specific form of treatment and that this should be carried on for some time after relief of the symptoms. It was our experience that giving liver by mouth and adding large amounts of vitamin D failed to cause any striking benefit. Furthermore, nicotinic acid, although given late in the course of the disease, caused no improvement in the patient's condition.

VITAMIN C CONTENT OF THE BLOOD IN NEWBORN INFANTS. DR. HEYWORTH N. SANFORD and DR. ARTHUR W. FLEMING (by invitation), Chicago.

Selection of a suitable method for study of vitamin C was made by a determination of the content of this vitamin in normal and in pathologic blood of adults. The micromethod of Farmer and Abt was used, with a weekly check by the macromethod. For 123 infants the average of 2 determinations made on the second and the eighth day of life was 0.753 mg. For 105 mothers of these infants the average was 0.884 mg., and for 51 miscellaneous adults the average was 0.99 mg. In a comparison of 72 mothers and their infants it was found that the amount of vitamin C in the blood of an infant is directly determined by that in the mother's blood and that the content in the infant's blood is approximately the same as in the mother's. The amount of vitamin C in the mother's blood has no influence on her production of breast milk, on the gain or loss of the infant or on the infant's weight at birth. The weight of the infant at birth does not influence the amount of vitamin C in its blood, but if the mother has an average amount of this vitamin in her blood a gain in weight by the infant when he is given her breast milk is followed by a small gain in the vitamin C content of his blood. A mother having a liberal vitamin C intake during pregnancy will show a high content of the vitamin in the blood after delivery, and this decreases in proportion as the mother's diet is deficient in vitamin C.

Seven infants that suffered from cerebral hemorrhage had a vitamin C content in the blood below 0.62 mg. All the mothers of these infants had a vitamin C content below 0.80 mg.

These findings indicate that the amount of vitamin C existing in the mother's blood depends on her prenatal diet, and this amount determines the quantity of the vitamin in the blood of her infant. The normal infant tends to have a content similar to the mother's. The infant of a mother with a low or threshold value of vitamin C in the blood may show a value lower than that of a normal person.

DISCUSSION

DR. LASLO KAJDI, Baltimore (by invitation): I had the privilege of seeing some recent work dealing with determinations of vitamin C in the blood of infants and of their mothers. In general it is true that the infant of a mother who has a good vitamin C intake will have a higher level of vitamin C than the infant whose mother's diet is poor in this vitamin. In a considerable number of infants this correlation was not found.

I wonder if in Dr. Sanford's cases the blood was taken during delivery or some days afterward; some investigators have reported that the level of vitamin C in the blood is definitely lowered during delivery.

My associates and I have followed the vitamin C levels and have found that it is not strictly correct to say that the level in the plasma corresponds to the amount in the depots of vitamin C in the body: If a child has an infection or if for some reason the intake is small and fever is present, the vitamin C level in the blood drops rather rapidly, giving the false impression that the child is in danger of scurvy.

We have been able, by parenteral injection of 200 mg. of vitamin C into an infant, to determine the level of vitamin C in the blood both before the injection and four or five hours afterward. In this way we established that a certain group of infants had scurvy, for in their cases the determination made after injection showed a rise of less than 0.16 mg. per hundred cubic centimeters. If we determined the vitamin C content of the plasma not after five hours but after twenty-four hours, we still found practically the same rise. For a second group of infants, who had previously had fairly large deposits of vitamin C in their bodies but who for a few days had not received adequate amounts of the vitamin, determinations made before injection showed just as low levels as for the children with scurvy; but those made after injection showed a much greater rise in the level (0.3 to 0.5 mg.). By this test we could distinguish the two groups.

DR. PHILIP C. JEANS, Iowa City: It may make a considerable difference whether the determinations are made in the first few hours of an infant's life, at the end of seventy-two hours or even some time later. I think the time of collection of the specimen may cause some difficulty in evaluating these data.

DR. ARTHUR ABT, Chicago: I am naturally in accord with what Dr. Sanford has said because he has used the method of Dr. Farmer and myself. We originally made the claim that the level in the blood follows the diet. We still hold that this is true except in cases in which absorption has been definitely interfered with. In a case of this type, such as Dr. Sission presented this morning, I should imagine that this general rule would hold. Dr. Alt, working on adults with achlorhydria at Northwestern University, was able to demonstrate such interference with absorption.

We have now worked out a method to determine the vitamin C content of the stool, although it is a difficult procedure. We believe that if a person in whom absorption is interfered with is given a diet adequate in vitamin C, more vitamin can be recovered from the stool than in the case of a normal person.

I cannot see why the newborn infant's blood should be different from that of its mother, because vitamin C is a crystalline substance which is diffusible through the placenta. It is generally recognized that in guinea pigs there is no synthesis of this vitamin. Zilva has shown that beautifully. He experimented on two sets of guinea pigs. The first set was given a diet high in vitamin C and the second a maintenance diet just above the scurvy level. He continued to administer these diets for a considerable period, and then on the same day he began to give both groups a scorbutic diet. One would not expect the first set to contract scurvy as soon as the second, but the disease developed at the same time in the two groups.

DR. THEODORE H. INGALLS, Boston (by invitation): I do not know why there should be any difference in the concentration of vitamin C in the maternal and in

the fetal blood, but there is. Such substances as calcium, phosphorus and nonprotein nitrogen have also been repeatedly demonstrated to be more concentrated in the fetal than in the maternal circulation.

I should like to comment on the question which has been raised in regard to cerebral hemorrhage. I do not believe that vitamin C deficiency has anything to do with the cerebral hemorrhage seen after delivery, though I think it plays an important role in that which occurs later in infancy, particularly in chronic pachymeningitis cerebralis interna haemorrhagica.

In the first place, the great majority of babies are born almost if not fully saturated with vitamin C, owing to the placental mechanism which causes a higher concentration of the vitamin in cord blood than in maternal blood. In the second place, it has been found that the concentration of vitamin C in the plasma is well below 0.5 or 0.6 mg. per hundred cubic centimeters before clinical signs of scurvy appear. Again, it takes considerable time for scurvy to develop. These facts explain why congenital scurvy is practically unheard of and why clinical scurvy is rarely seen before the age of 3 months.

If a baby saturated with vitamin C is nursed solely on pasteurized milk the ascorbic acid level of the blood will drop to around 0.3 mg. per hundred cubic centimeters by the end of the second week. Although this figure indicates depletion of vitamin reserves in the blood, in the liver and in other tissues, it seems to take a considerably longer time for the histologic and clinical changes of scurvy to be effected. My opinion is that the valuations shown are not low enough to be significant, that definite vitamin C deficiency is rarely found in the newborn and that the forces of labor, prematurity and possibly hemorrhagic disease of the newborn are the important factors involved.

DR. CHARLES H. SMITH, New York: Is it necessary to give orange juice to a baby who has a good supply of breast milk? I have been criticized for teaching that it is not.

DR. HENRY J. GERSTENBERGER, Cleveland: The finding of the authors that Negroes have a relatively high ascorbic acid level suggests that possibly the dark race can economize in the use of this vitamin better than the white race can. An experience which my associates and I recently had may speak in favor of such a view. A Negro woman weighing about 220 pounds (100 Kg.) produced milk which contained about 20 mg. of ascorbic acid per liter. After this level had been maintained for a number of days, it suddenly dropped to a much lower value and then rose nearly to its previous high point. When we tried to obtain an explanation for this occurrence, the mother stated that the only change she had made in her diet was that she had not eaten her customary number of "little apples;" oranges, potatoes and tomatoes, she maintained, were not included in her list of foods.

DR. HEYWORTH N. SANFORD, Chicago: I did not mention, as I should have, that the blood was taken from the mother at the same time that it was taken from the baby, on the second and the eighth day. We did find certain slight differences between these intervals, but those are averaged on the tables. I agree with Dr. Kajdi that a number of factors influence the amount of vitamin C in the blood. One cannot deduce from 1 or 2 specimens that there is or there is not scurvy. The findings will vary from day to day. It is true that infection will decrease the level temporarily. Dr. Jeans stated that the age of the premature infant may make some difference. The ages of these premature children varied from 1 to 24 days. Three infants were under 1 week of age, 2 were between 1 and 2 weeks of age and 1 was 24 days old, and those low figures held good all the way through.

I was interested in Dr. Ingall's remarks concerning cerebral hemorrhage. I did not say that deprivation of vitamin C for three days will cause cerebral hemorrhage; but I do want to point out that if certain mothers have a low vitamin C content in the blood their babies will also, and in 8 cases of cerebral

hemorrhage this was consistently true. These babies were not deprived of vitamin C for two or three days, but on account of the inadequate diet of the mother they suffered from a deficiency of vitamin C throughout the period of gestation.

Regarding Dr. Smith's question about giving orange juice to a breast-fed baby, that depends on the mother's vitamin C intake before and after delivery. If her blood has ample vitamin C and if she has a good intake during the time she is nursing her baby, there will be a slight rise in the vitamin C content of the baby's blood during that time, and it should not be necessary to give the baby orange juice.

VIRUS IN THE STOOL IN ABORTIVE POLIOMYELITIS. DR. JOHN R. PAUL (by invitation), DR. A. J. VIGNEC (by invitation) and DR. JAMES D. TRASK, New Haven, Conn.

The title of the paper is designed not so much to call attention to another instance of the detection of virus in fecal material as to emphasize the mild type of illness in which this happened.

In a small epidemic of poliomyelitis last fall, we made 22 attempts to demonstrate the virus in nasal washings and in stools of patients with abortive and paralytic forms of the disease. The results were positive in 4 cases of the abortive form and negative in the others. Three of the positive results represented the 3 instances in which nasal washings were obtained within thirty-six hours after onset. In the fourth case, in which the result was positive, the early nasal washings were lost and the virus was found in the stools on the first, the thirteenth and the twenty-fourth day after onset.

In 1 of the samples of stool held in the refrigerator the virus was demonstrable after eleven days and in another sample after seventy-four days. From 1 sample of stool the virus was precipitated with acetone. The stability and persistence of the virus in feces seem unequivocal.

This report describes, therefore, an example of a convalescent intestinal carrier, and it calls attention to the epidemiologic importance of the abortive form of the disease, which can be recognized by its occurrence in relation to cases of the frank form or by animal inoculation.

DISCUSSION

DR. FRITZ TALBOT, Boston: This method of approaching the infectiousness of poliomyelitis is interesting. A child who in the summer had been living in the Southern states, where there was an epidemic of poliomyelitis, came east. After about twelve or fourteen days symptoms and signs of poliomyelitis developed. The girl had mild involvement with slight paralysis, which disappeared. The interesting point in her case was that the whole summer colony was much upset, and the girl's physicians and her parents had a heart to heart talk with her. She was 17 or 18 years old. She had been to a dance the night before the symptoms appeared, and the adults felt that they should know who were the possible suspects in the community. They told her it was important to let them know every one she had come in close contact with, particularly every one she had kissed in the last twenty-four hours. The list contained the names of 2 girls and 6 boys. None of them contracted poliomyelitis. It seems to me that that was a pretty experiment on the possible contingencies of the acuteness of the disease. Maybe Dr. Trask could explain why these people did not get the disease.

One or two of the physicians here want to know exactly what Dr. Trask means by "spine sign."

DR. JOHN A. TOOMEY, Cleveland: When the virus of poliomyelitis is injected intravenously into monkeys, it can occasionally be recovered from the stool. I have been able to do this by concentrating the virus in the Flosdorf-Mudd lyophile apparatus.

DR. JAMES D. TRASK, New Haven, Conn.: In regard to Dr. Talbot's question about the spine sign, it is elicited as follows: One sits the child upright with legs extended and attempts to make him touch the forehead to the knees. Abnormal stiffness constitutes a positive spine sign.

I think it is important that Dr. Toomey has been able to recover the virus in the stool of the monkey.

FURTHER STUDIES ON EPIDEMIC INFLUENZA. DR. JOSEPH STOKES JR., DR. AIMS C. MCGUINNESS (by invitation), DR. PAUL H. LANGNER JR. (by invitation) and DOROTHY R. SHAW (by invitation), Philadelphia.

Successful parenteral vaccination of animals against influenza with the active influenza viruses of swine and of human beings was originally done by Shope and later by Smith, Andrewes and Laidlaw. This led to the studies on the intramuscular vaccination of human beings with active human virus which have previously been reported (*J. Clin. Investigation* **16**:237 [March] 1937; *Am. J. M. Sc.* **194**:757 [Dec.] 1937).

It became important to determine whether the viruses isolated early in 1937 from persons in two state colonies gave evidence of cross neutralization and cross immunization with the human virus PR-8 of Francis, which was used for vaccination of one third of the members of these colonies. Evidence was obtained which confirmed the fact that protection was afforded the vaccinated persons.

Serums from herds of swine attached to three colonies were tested originally by Shope and later at the Children's Hospital for neutralizing properties, particularly against the viruses isolated at the Children's Hospital from two of the colonies. Serums from old swine attached to the colonies during the epidemic of influenza (1937) showed neutralizing properties against a variety of human virus strains but not against a swine virus strain (S-15 of Shope). Serums from young pigs which were bought well after the epidemic but kept in the same herds as the old swine showed no neutralization against either the human or the swine strains. The serums of the old swine showed slight differences in their neutralizing power against the two strains of human influenza virus isolated early in 1937 in two colonies, which probably indicated slight antigenic differences in these viruses. Cross immunization, however, was obtained with all the strains of human virus studied, including the English W.S. and the Australian-Melbourne strain.

DISCUSSION

DR. JAMES D. TRASK, New Haven, Conn.: I should like to ask Dr. Stokes if he noted any unpleasant reactions from repeated injections of vaccine.

DR. HORACE L. HODES, Baltimore: I should like to ask Dr. Stokes how large a quantity of virus must be given subcutaneously to mice to immunize them. How much larger is the vaccinating dose than the intranasal minimal infective dose? The dose used for immunization appears to be of importance in the case of some viruses; unless a minimal vaccinating quantity is injected, no immunity results. Is this also true of the influenza virus?

DR. JOSEPH STOKES JR., Philadelphia: I am glad Dr. Trask mentioned Dr. Francis' results. Of the 39 strains of virus isolated in the 1936-1937 epidemic in England, only 1 strain showed significant differences in neutralization experiments. This does show the importance of using different strains of virus in such vaccines. During the past year my associates and I have used both the Melbourne and the English strains in the preparation of the vaccines.

We have noted only 1 reaction with over 12,000 intramuscular injections of vaccine. In this instance a woman was given vaccine at the time she was contracting an infection of the upper respiratory tract. She went through an illness which was somewhat similar to influenza although not severe. After this there

developed a fourfold increase in complement-fixing antibodies. There may have been some relation between the virus injected and the disease.

We have not determined the exact amount of the dose necessary to give immunity.

FACTORS AFFECTING THE NITROGEN BALANCE IN THE PERIOD OF GROWTH. DR. JOSEPH A. JOHNSTON and DR. JOHN W. MARONEY (by invitation), Detroit.

The effect of the removal of a focal infection (tonsils) unaccompanied by fever was studied by means of continuous determinations of the nitrogen balance and of the basal metabolic rate. Nine children were observed. A slight fall in the basal metabolic rate and a marked increase in the retention of nitrogen were observed. It was concluded that the effect of infection on retention of nitrogen was not understandable in terms of the altered metabolic rate but rather that there was involved an element of what Peters and Van Slyke termed toxic destruction.

The effect of administering thyroid to the cretin was anabolic; a rising metabolic rate was accompanied by increased retention of nitrogen. With extremely high rates associated with hyperthyroidism a tendency to a negative balance existed, but it could easily be offset by increasing the intake of calories derived from fat and carbohydrate. One subject just in balance was given a small dose of thyroid (¼ grain [0.015 Gm.] Burroughs Wellcome), and this was followed by increased retention of nitrogen.

A continuous balance for two and one-half months before and for three months after the menarche showed that the retention was strikingly high in the period before and diminished markedly in that following the first menstruation. The basal metabolic rate was slightly higher before than after the menarche.

RELATION OF NUTRITION TO GROWTH OF BONE. DR. ALFRED T. SHOHL, Mirror Lake, N. H.

The composition of bone and of the body may be expressed in terms of chemical equivalents both for the solid phase and for the water phase. Such an analysis discloses the distribution of minerals in the body and shows that the preponderance of base is situated in the skeleton. It further shows that nearly one tenth of the extracellular water is situated here. Of the fractions of solid, lime salts and water, the water is the greatest, even in adults.

As to the requirements of calcium and phosphorus for normal growth and development, study of food intakes and of metabolic measurements has given only data serving for orientation. An ideal standard may be sought by analysis of the body at various ages (Herter's method).

By means of a plot of the growth of the body and of the skeleton it is possible to estimate the amounts of calcium and of phosphorus which are required daily for normal osseous development.

The relation of the calcium to the phosphorus intake shows that retentions are proportional both to absolute intake and to the calcium-phosphorus ratio. Rickets may be produced at any ratio, provided the intake is low.

Citric acid and sodium citrate have been shown to affect favorably the development of bone.

DISCUSSION

DR. DANIEL C. DARROW, New Haven, Conn.: Ordinarily in speaking of bone salts it has been the custom to speak of the calcium, the magnesium and the phosphorus carbonate content. I think it has been shown that all forms of calcification that have been studied contain sodium as well. I do not believe calcification can occur without the presence of 1 sodium molecule to 30 molecules of calcium.

DR. BENGT HAMILTON, Chicago: In respect to growth of bone, one gets the idea from Dr. Shohl's paper that for a certain amount of growth a certain degree of retention of calcium is necessary. I wonder if Dr. Shohl agrees with me that there is in osseous growth greater elasticity than that idea would indicate, as the human body can show rapid growth of bone with varying retentions of calcium.

DR. PHILIP C. JEANS, Iowa City: A study such as this is of extreme importance in the determination of the mineral requirements during the period of growth. A great deal, however, depends on the criteria used in the analysis. There is a good deal of osteoporosis during adolescence, and senile osteoporosis is so common that it is almost physiologic. Recognizing the extent to which the bones of adults may be lacking in proper calcification, one should take precautions as to standardization of criteria. Dr. Shohl has said that his figure is lower than that used by my co-workers and me; in fact, his amount of 1,200 Gm. is somewhat less than the 1,500 Gm. we should consider as minimal; we should prefer 2,000 Gm. as a safer average. This amount of retention can be reached easily by adding 1½ pints (710 cc.) of milk and a little vitamin D to an otherwise good diet.

DR. L. EMMETT HOLT JR., Baltimore: I am somewhat perplexed by Dr. Shohl's first slide, which seems to indicate that practically all of the body phosphorus is in the bone. I may have misinterpreted his data, but I was under the impression that a considerable part of the body phosphorus was present in other tissues. I should appreciate it if Dr. Shohl would interpret this slide more fully.

DR. JOSEPH A. JOHNSTON, Detroit: I should like to point out to Dr. Shohl that in the case just presented the average calcium retention for three months preceding the menarche was approximately 500 mg. a day and that after the first menstrual period it fell to approximately 300 mg. per day for the next two and a half months.

DR. ALFRED T. SHOHL, Mirror Lake, N. H.: Dr. Darrow was right in saying that the appetite minerals do include sodium, but it is usually not considered an essential factor.

In regard to the question of Dr. Hamilton as to whether bone has some latitude in its rate of growth, I think that it does. I think all the organs have mechanisms to protect themselves, and one is that the bones can utilize their available excess supply of calcium by storing it in the trabeculae so that there is an excess in the bone without harm; one can probably have a diminished amount in the bone without great harm provided the vitamin intake is liberal. According to Sherman's idea, one will reach the same end point, regardless of the rate of growth; the point is, what is the desirable rate?

With regard to Dr. Jeans's standards, I cannot enter into a practical discussion of the reasons that led me to do this work and of the methods I have used, but the easiest way to ascertain the amount of calcium in the bone is based on the age of the body. Dr. Jeans standard has been based on the precarious water content of the bone and not on analysis of calcium.

Dr. Holt is undoubtedly correct about the phosphorus in the body; it is true that a considerable proportion of the total phosphorus is not present in the skeleton, but I mentioned that I was allowing 0.3 for the valence of phosphorus.

In regard to Dr. Johnston's statement, of course there are many other factors I did not mention which have an effect on the retention of calcium. I do not know the effect of the sexual cycle in girls, but that is a factor outside the ones I have discussed.

Final Session

Saturday Morning, May 7

ELECTROLYTE DEFICIT IN A PATIENT WITH SEVERE BURN TREATED BY CONTINUOUS TUB. DR. DANIEL C. DARROW, New Haven, Conn.

A boy of 3 years who had an extensive burn was seen after treatment for about sixty of sixty-four hours in a continuous tub containing salt. At this time

the serum bicarbonate was 11 and the serum chloride 80 milliequivalents per liter. With a continuous intravenous drip of sodium chloride and sodium bicarbonate improvement was rapid. During the next eight days the patient was treated with methylrosaniline (gentian violet). The crusts were then soaked off with saline dressings and a continuous saline tub. The tub was used only a few minutes on the eighth day, about nine of twelve hours during the ninth day (but not at night) and about four hours on the tenth day. At 4 p. m. the child was again in collapse and appeared dehydrated. At this time the serum bicarbonate was 20 and the chloride 69 milliequivalents per liter. Recovery was again prompt with a continuous intravenous drip of sodium chloride and sodium bicarbonate.

The patient showed symptoms and signs of dehydration associated with low concentration of base and chloride. Probably no actual dehydration existed, but rather a shift of water into the cells in response to diminution of extracellular base. During the first two days the patient had two convulsions, which were relieved by hypodermoclyses of saline solution while he was being treated in the tub. These convulsions were probably analogous to those of water intoxication, for in this condition actual or relative deficit of sodium is the cause of the intoxication. Since the solution in the tubs was found to be not over one-third physiologic, the loss of extracellular electrolyte is explained by the diffusion of sodium and chloride from the areas denuded of skin by the burns. The case illustrates an important means of losing salt and again emphasizes the fact that loss of extracellular electrolyte rather than of water is the chief factor in so-called dehydration.

DISCUSSION

Dr. Allan M. Butler, Boston: I missed the concentration of sodium on the third day, which Dr. Darrow said was low. Possibly he did not give the numerical value. I should be interested to know the specific concentration. Dr. Darrow has emphasized the use of sodium bicarbonate. In the Children's Hospital in Boston my associates and I have stopped using sodium bicarbonate; we use sodium lactate because of the ease with which the latter can be made up and because of its availability on the market. I wonder if Dr. Darrow would like to express an opinion as to whether there is an advantage in the use of sodium bicarbonate or whether sodium lactate might be used just as well.

Dr. Alfred T. Shohl, Mirror Lake, N. H.: I noticed that one method of administrating sodium chloride was oral. I wonder what Dr. Darrow's position is in regard to the advantage of giving sodium chloride by mouth.

Dr. George M. Guest, Cincinnati: Damage to the adrenals during the intoxication produced by burns is often cited as an important part of the pathologic picture. Do you believe that this factor, as well as the loss of sodium chloride into the burned area, can change the concentration of sodium chloride in the serum?

Dr. Glenn E. Cullen, Cincinnati: I should like to make one point about the treatment of burns. During the World War, when my co-workers and I were working with burns, we had occasion to treat many of them with a hypertonic dilute solution of sodium hypochlorite (Dakin's solution). We talked a great deal about it at that time and were well satisfied with it. I burned myself severely with a high voltage current, and after trying everything else suggested I put my hand into a large tub of solution of sodium hypochlorite. The relief of pain was so immediate that we proceeded to try it in a series of cases; the results were amazing. The pain goes away immediately, and the burn clears up beautifully. I have been disappointed that this solution has not been used much since.

In these cases no analysis was made of the electrolyte concentration in the blood, but Dr. Darrow's experience suggests that in any continuous use of solution of sodium hypochlorite the electrolyte balance should be determined. The probable result would be concentration rather than dilution of blood.

Dr. Daniel C. Darrow, New Haven, Conn.: There was not enough blood for the initial determination of sodium. However, the low level of bicarbonate and of chloride indicated that the sodium was correspondingly low.

As to the types of solution used subcutaneously or intravenously in the treatment of burns, I have used a solution of sodium chloride and sodium bicarbonate resembling interstitial fluid. For a time I prepared it myself, but recently it has been made by a chemical company. I prefer a solution containing bicarbonate to one containing lactate not because there is any ultimate difference in the metabolic effect but because a solution resembling interstitial fluid is less irritating locally. In the treatment of salt deficit, physiologic solution of sodium chloride is satisfactory in most cases. When acidosis is present, a solution containing sodium bicarbonate or sodium lactate as well as sodium chloride has many advantages.

THE ANTISTREPTOLYSIN TITER OF THE SERUM IN ACUTE GLOMERULONEPHRITIS. DR. JOHN D. LYTTLE, DR. DAVID SEEGAL (by invitation), DR. EMILY NICHOLS LOEB (by invitation) and DR. ELIZABETH L. JOST (by invitation), New York.

The periodical literature and textbooks list the most heterogeneous types of infection and other conditions (such as influenza, diphtheria, measles, the common cold, sore throat, exposure, osteomyelitis, pregnancy, intestinal catarrh and pyoderma) as prodromal episodes in cases of acute glomerulonephritis. For this reason and because at the time the patients are first observed (at the onset of the nephritis) the clinical and bacteriologic evidence of the preceding infection may be inadequate, it seemed desirable to obtain more specific evidence on the character of the infection which precedes nephritis. A preliminary study in 1933 showed that of 22 patients with acute glomerulonephritis the serums of 20 had a definite increase in antistreptolysin titer. The present report is a more complete study of this antibody in a larger group of patients, who were observed over a period of four years.

There is general agreement that the antistreptolysin level in persons who have been free of hemolytic streptococcic infection is less than 100 units; after such infection the antistreptolysin titer rises, and high titers may be maintained for some time after the infection has subsided. The rise in titer may be moderate in degree and of brief duration, and it may be shown only when determinations are made for a period before and after an infection in order to obtain the natural or basal level. In other words, the antistreptolysin titer of a person taken at random may be difficult to interpret, but if serial studies are made interpretation is more accurate and the significance of moderate elevation of titer is clearer. For our purpose we considered an antistreptolysin titer of 125 units or more as evidence of recent infection with hemolytic streptococci if previous or subsequent determinations showed the level to be lower.

This report is based on a study of 116 consecutive and unselected cases of acute glomerulonephritis observed at the Babies' Hospital and the Presbyterian Hospital from March 1933 through May 1937. In 83, or 71.5 per cent, of the 116 cases there was bacteriologic evidence of infection with hemolytic streptococci, while in 33, or 28.5 per cent, there was negative bacteriologic evidence of this type of infection.

Careful study of our clinical and immunologic data indicates that during the acute stages of glomerulonephritis the maximum antistreptolysin titer (1) is not related to age or sex, (2) has no relation to the severity or duration of the nephritis but (3) is definitely related to the type and severity of the acute infection which precedes or accompanies the acute nephritis.

The data presented here establish the fact that, in spite of the heterogeneous group of prodromal infections observed and the many cases in which the history and clinical evidence of the preceding infection were unsatisfactory, in 94 per cent of 116 consecutive cases of acute glomerulonephritis the patient showed specific immunologic evidence of a recent hemolytic streptococcic infection.

The maximum antistreptolysin titer was present at the onset or during the first few weeks of the attack of acute nephritis, but the significance of his fact is not apparent. The maximum rise in antistreptolysin titer was of all degrees, and the clinical findings in the patients in whom extremely high antistreptolysin

titers developed were not different from those of patients in whom there was a moderate or intermediate rise in titer. There was a wide variation in the curve of antistreptolysin response which was constructed over a long period. The form of the curve had no relation to the severity or duration of acute nephritis or to the tendency to contract chronic nephritis.

DISCUSSION

Dr. James D. Trask, New Haven, Conn.: The experience of my associates and myself with antistreptococcic titers is similar to that of Dr. Lyttle: We commonly found high values during convalescence from suppurative streptococcic lesions.

Daily Water Exchange of Premature Infants. Dr. S. Z. Levine and Dr. H. H. Gordon (by invitation), New York.

The daily water exchange of 6 healthy premature boys from 14 to 18 days old and weighing from 1,600 to 2,650 Gm. was determined in 33 observations for a total of eighty-two days under varying conditions of diet and environment. The infants were studied in an air-conditioned room which permitted rigid control of external conditions, and all sources of incoming and outgoing water were determined by chemical analysis and from the composition of the metabolic mixture.

Three methods were concurrently employed for measuring the water exchange: The direct metabolic method of Newburgh, the indirect metabolic method and the electrolyte method of Gamble, Peters and Darrow. The similar results obtained by all three methods provided evidence of the reliability of the observations.

The results may be briefly summarized as follows:

Diets customarily employed in the feeding of premature infants and containing about 140 to 160 Gm. of water per kilogram of body weight per day (2 to 2½ ounces per pound) provide for adequate retention of water within the body (60 to 70 per cent of the total accretion in weight). In terms of percentages of water intake, the partition of outgoing water through the different avenues of elimination with these diets averaged 59 per cent through urine, 6 per cent through feces and 29 per cent by way of skin and lungs. The remaining 6 per cent of available water was retained in the body for growth. The distribution of water output of these subjects differs markedly from that of full term infants given comparable diets, particularly in the lower quota of insensible output and in the reciprocally higher urinary output.

Augmentation of the daily fluid intake above the level of 120 Gm. per kilogram is not usually accompanied by an increase in water balance, the extra water of the diet being almost quantitatively eliminated in the urine. Reduction of fluid intake below this threshold is often associated with a negative water balance, and when the intake is reduced below 100 Gm. per kilogram clinical dehydration may ensue, with the development of dehydration fever.

Elevation of either the surrounding temperature or the relative humidity is associated with markedly augmented loss of water from skin and lungs and with a reciprocal decline in the urinary output of water. The net result in terms of water balance depends on the level of environmental temperature and humidity and on the level of fluid intake.

These studies are being continued to establish, if possible, conditions of diet and environment which may be considered optimal for premature infants.

DISCUSSION

Dr. Irvine McQuarrie, Minneapolis: One of my associates intends to make a similar study, and we are anxious to know the critical temperature for sweating for a baby and how it is determined, whether by a chemical test or otherwise. There may not be enough sweating to be visible over large parts of the surface. I wonder if young babies do perspire at the same temperature as the older chil-

dren; we have found that older children perspire at about 74 degrees under ordinary atmospheric conditions.

DR. DANIEL C. DARROW, New Haven, Conn.: This is irrelevant but it has been reported that the retention of minerals is greater with feeding of cow's milk than with human milk because of the greater content of minerals in cow's milk. I think that is unlikely, except for calcium and phosphorus. I wonder if Dr. Levine has any figures on potassium and calcium.

DR. HAROLD L. HIGGINS, Boston: The decision as to the optimum room temperature for premature babies brings up the question of conduction and radiation. If a premature infant is near a heated metal tank or other warm radiant surface, he is going to absorb heat from the tank; he will be quite comfortable and will get along perfectly well, even though the temperature of the room is below 70 F. It seems to me that the baby's water exchange will depend on his opportunity to pick up heat by radiation from the outside or to give off heat to a cold surface.

DR. ALFRED T. SHOHL, Mirror Lake, N. H.: Have you taken concentrations of food into consideration, so that one may know under what dietary conditions dehydration takes place?

DR. SAMUEL Z. LEVINE, New York: Our rooms for premature infants contain a unit which maintains constant temperature and humidity. In some of the observations reported it was our purpose to study the effect of variations in humidity; infants were exposed successively to 40 and to 80 per cent relative humidity. We have not yet performed the crucial observation of subjecting premature babies to a constant temperature of 77 degrees with humidities varying between 40, 65 and 80 per cent, but I think there would be a slightly higher output of water through the skin and lungs at a high humidity, all other external factors remaining constant.

In answer to the question of Dr. McQuarrie, I do not believe that there is a rigid threshold for sweating in premature infants. They may show visible perspiration at varying levels of external temperature, more frequently at feeding than at other times. The method we used to determine sweating was the Vasti test, which consists of applying a piece of filter paper to the surface of the skin, then saturating it with silver nitrate and exposing it to the light. If it turns black, it indicates the presence of chloride and probable activity of the sweat glands. This test has been found to be positive at temperatures as low as 72 F., but it varies a good deal not only with premature infants but with those born at full term.

In relation to Dr. Darrow's statement about supermineralization, the few calculations which we have thus far made indicate that there is no supermineralization with sodium or other constituents except calcium and phosphorus. Since the calcium content of cow's milk is high, premature infants retained appreciably more calcium when taking this food than when receiving human milk.

Dr. Higgins' point is well taken. We have attempted to keep the extraneous conditions uniform in regard to radiation. The cutaneous temperature was recorded at least five or six times daily throughout observations and was correlated with the rectal temperature and with the temperature of the objects surrounding the infant.

Dr. Shohl asked about the relation between ingested organic foods and water and the production of fever. I believe this varies with individual subjects, but these premature infants all had fever when they received from 60 to 70 Gm. per kilogram of body weight of water as water and their ordinary chlorine and protein intake. When the daily water intake was between 90 and 100 Gm. per kilogram, considerable body water was lost, but fever did not develop.

ABSORPTION OF CALCIUM SALT FROM INTRACUTANEOUSS INJECTIONS IN NORMAL AND IN ABNORMAL RATS. DR. BENGT HAMILTON and DR. MARGARET M. DEWAR (by invitation), Chicago.

The intracutaneous injection of 0.5 cc. of a solution of calcium gluconate containing 5 mg. of calcium has a strikingly different effect in rats given different

diets. When the animals are fed an adequate diet (Bill's diet) the injection leads to a marked inflammatory reaction, in many cases to hemorrhage and necrosis. There was little or no reaction in animals given the following diets: McCollum's rachitogenic diet; the same diet with the addition of 2 per cent cod liver oil; a normal stock diet (Bill's diet) with 0.5 per cent beryllium carbonate; a normal stock diet (Bill's diet) with calcium carbonate in an amount sufficient to make the calcium-phosphorus ratio 5 : 1 and a diet of whole corn. When the McCollum rachitogenic diet was administered with sodium biphosphate U. S. P. in amounts sufficient to make the calcium-phosphorus ratio 1 : 1, the results were similar to those obtained with a normal diet.

The animals on the McCollum rachitogenic diet and those on the stock diet with berryllium carbonate showed roentgen evidence of rickets; the others did not.

Analysis of the tissue at the site of injection showed that in the normal animals a considerable part of the injected calcium remained after twenty-four hours, while in the others most of it had been absorbed. The absorption was most complete when the McCollum rachitogenic diet was given.

There was a certain amount of parallelism between the concentration of phosphorus in the serum and the rate of removal of calcium from the skin: When the serum phosphorus was low, the calcium was always rapidly removed. Possibly there was also some relation to the level of serum calcium.

DISCUSSION

Dr. George Guest, Cincinnati: Do you have an analysis of the phosphorus content of the skin of these animals as well as of the calcium content?

Dr. Irvine McQuarrie, Minneapolis: I should like to ask if Dr. Hamilton has done any experiments to determine whether there is absorption from the peritoneal cavity.

Dr. Bengt K. Hamilton, Chicago: I shall have to answer both questions in the negative. The amount of skin we get from each animal is so small that we have not had enough to make a study of the phosphorus content of the skin. In answer to Dr. McQuarrie, we have made no determinations as to the possible absorption from the peritoneal cavity.

Sodium Chloride Balance. Dr. J. L. Gamble, Dr. C. Fan (by invitation) and Dr. F. W. Barnes Jr. (by invitation), Boston.

According to recent evidence, the sodium and the chloride ion occupy an exclusively extracellular position in the body. The sodium chloride balance therefore rests on the mechanisms which control the volume of extracellular fluid. With a stationary intake of sodium chloride and a roughly constant rate of loss of it in the stools and in the sweat, fluctuations in the daily excretion of chloride in the urine should closely parallel change in the volume of extracellular fluid. Evidence of this relationship is found in change in volume of urine and in body weight. Such data were obtained from several adult subjects whose intake of water and food was constant, with change only in the level of intake of sodium chloride. These data make it clear that sodium chloride balance is subject to large oscillations and that adjustment to a change of level of intake is a protracted process.

DISCUSSION

Dr. Irvine McQuarrie, Minneapolis: I wonder about the part posture and activity play in this balance. There is a considerable difference between daily and nightly activity; there is more activity during the day, and in our own studies on mineral balances my associates and I observed marked differences between the daily and the nightly output of sodium chloride as well as of water.

Dr. James L. Gamble, Brookline, Mass.: This study is based on consecutive twenty-four hour values for chloride obtained from subjects who were following

their usual routine of laboratory work. Their physical activities and hours of sleep were approximately constant. Presumably the influence of posture on these daily values did not vary widely.

CONVULSIVE MECHANISM IN IDIOPATHIC HYPOPARATHYROIDISM. DR. M. R. ZIEGLER (by invitation), DR. ARILD E. HANSEN (by invitation) and DR. IRVINE MCQUARRIE, Minneapolis.

The lack of close agreement between the absolute level of serum calcium and the occurrence of convulsions in the parathyroprivic and in the infantile type of tetany indicates the need for further information regarding the factors involved in the convulsive mechanism in these conditions. A state of latent tetany may frequently be changed to one of manifest tetany by reduction of the hydrogen ion concentration or by increase in the level of inorganic phosphorus, presumably because these procedures cause reduction in the calcium ion concentration. However, alterations in the blood p_H and in the carbon dioxide and inorganic phosphorus content of the plasma just prior to the onset of convulsions have never been demonstrated. The mechanism by which an acute infection brings on convulsions in the presence of latent tetany is still obscure.

With the hope of obtaining a clearer understanding of the convulsive mechanism in hypoparathyroidism, we attempted to ascertain the degree of correlation between changes in the serum electrolytes and in the water and mineral balances on the one hand and the occurrence of convulsions on the other. We determined the effects of a variety of experimental procedures or conditions, such as changes in the mineral content of the diet, alteration in the water intake, voluntary hyperventilation of the lungs, intravenous administration of typhoid vaccine, induction of fever by diathermy and sustained pituitary antidiuresis.

After the patient had been kept on an extremely low mineral intake for some time, convulsions were readily induced by hyperventilation, by the intravenous injection of typhoid vaccine and by sustained pituitary antidiuresis. These procedures failed to produce convulsions, however, when the mineral content of the diet was comparatively high. Administration of extra sodium chloride reduced the convulsive tendency but did not entirely prevent seizures after repeated injections of pitressin during the period of low mineral intake. Under similar dietary conditions, convulsions did not occur as a result of administration of pitressin when parathyroid extract was also administered. Diathermy fever maintained for a number of hours caused a slight increase in irritability but failed to induce convulsions, even when the mineral content of the diet was extremely low. Prolonged administration of sodium bicarbonate in doses of 6 Gm. daily during the period of high mineral intake failed to provoke convulsions, even when the patient was also subjected to the pitressin and the intravenous vaccine test. Except for the increase in calcium and the decrease in inorganic phosphorus resulting from the administration of parathyroid extract, the procedures used appeared to have little or no significant effect on the levels of these elements in the serum. The results suggest that retention of water by the central nervous system without a corresponding retention of minerals plays an accessory role in the convulsive mechanism in this type of tetany, as claimed by Baar and by Ellis. Without necessarily altering the levels of serum calcium and inorganic phosphorus conspicuously, the high mineral diet apparently suffices to protect the nervous system against such retention of water. The beneficial effect of parathyroid extract in parathyroid tetany appears to depend on its dehydrating action as well as on its more specific function of regulating calcium and phosphorus metabolism.

DR. DANIEL C. DARROW, New Haven, Conn.: Now physicians must start over again on the question of tetany. The chemical changes are not entirely changes of extracellular fluid, although all the factors which Dr. McQuarrie mentioned are important. Nevertheless, there must be some change in the cells, since the various changes in extracellular fluid associated with tetany can no longer be explained as causing tetany through their effect on calcium ion concentration.

INFLUENCE OF AGE ON VENTRICULAR DISPLACEMENT IN THE HEMIPLEGIAS OF CHILDREN. DR. BRONSON CROTHERS, Boston.

Encephalography is an accepted method of investigation in neurologic clinics. In general, every one believes that it is a procedure of great value in diagnosis and prognosis, but there are a few situations in which gross errors are possible if the factor of growth and development is ignored or underemphasized.

It is obvious that displacement of the ventricular system is a common and highly important finding. The usual explanation is that the ventricles can be pulled by retraction or pushed by new growth or by fluid. In this paper is considered the uneven growth of the cerebral hemispheres as a factor in displacement. A random series of encephalograms showing displaced ventricles was collected. Cases in which there were tumors or other active lesions were excluded. In the remainder the displacement was considered in relation to the age of the child at the time of the original cerebral accident and in relation to the time between the accident and the time of encephalography.

In general the evidence suggests, although it does not prove, that displacement is frequently due to uneven growth of the two cerebral hemispheres. If further study confirms this initial suggestion, a certain shift of emphasis in interpretation of encephalograms of children may be desirable.

DISCUSSION

DR. CHARLES G. KERLEY, New York: Dr. Crothers has established a diagnostic procedure in the case of the hemiplegic patient that may be employed in explaining to the distressed parents the nature of the child's ailment. It is usual for parents of children of this type to travel about from one physician to another in the hope of finding one who will give them encouragement as to the child's future. I advise all such parents to have this roentgen study of the brain carried out which on inspection will enable them to appreciate the hopeless state of the child.

I should like to ask Dr. Crothers at how early an age the child may be safely subjected to the procedures necessary in making the encephalogram.

DR. BRONSON CROTHERS, Boston: The point that I wanted to make is that the standards for infants are inadequate. Some bad errors have been made with babies. I have carried out this procedure on a baby aged 3 months, and it has been done on younger infants. The one time that the risk seems appalling is when the procedure is really justified, and that is when one expects to find a tremendous defect. Although encephalography is dangerous, it is justifiable, but I think we need standards in the case of babies.

DR. CHARLES G. KERLEY, New York: Can one do any permanent harm to a baby by carrying out this procedure?

DR. BRONSON CROTHERS, Boston: I think there is danger of being told that one has done harm. I have seen no damage beyond the usual fatalities, except that occasionally a dormant process is accelerated.

Book Reviews

Parasitology with Special Reference to Man and Domestic Animals. By Robert Hegner, Ph.D., Professor of Protozoology, Johns Hopkins University; Francis M. Root, Ph.D., late Associate Professor of Medical Entomology, Johns Hopkins University; Donald L. Augustine, Sc.D., Assistant Professor of Helminthology, Harvard University, and Clay G. Huff, Sc.D., Associate Professor of Parasitology, University of Chicago. Price, $7. Pp. 833, with 308 illustrations. New York: D. Appleton-Century Company, Inc., 1938.

This is a revision of "Animal Parasitology," which was published under the same authorship in 1929. The title has been changed to "Parasitology" because the former title had led some to believe that the text related only to the parasites of lower animals. Man and his parasites come in for a full share of attention, although the parasites of common domestic animals are included, as well as the parasites of a few other species of animals, which serve as a source of material for study.

The book opens with a 33 page introduction by the senior author. He discusses the general biology of parasitism, host-parasite relations and changes produced in the host and in the parasite. The body of the volume is divided into three main sections: "Protozoology," by Hegner; "Helminthology," by Augustine, and "Arthropods of Parasitological Importance," by the late Professor Root, revised by Huff.

The book discusses parasitology from the standpoint of the parasites as living animals. It is therefore, as it should be, a zoologic treatise which has to do with the classification, the morphology and, most important of all, the life cycles of parasites. But it is not to be inferred that the host is neglected. The spread of infection to man and from man, diagnosis and treatment are briefly but amply considered. The important field of prevention of infection by animal parasites is covered. While the book is not a manual of laboratory technic, essential procedures are described.

References to the literature are brought together into a section of 79 pages under the three headings which divided the subject matter. An author index and a subject index follow.

This is a valuable text for students of parasitology and an important reference work for the physician or veterinarian who seeks authentic information in a difficult field. The book is one of "The Century Biological Series," of which Hegner is the editor.

The Life of Chevalier Jackson. By Chevalier Jackson. Price, $3.50. Pp. 229, with 80 illustrations. New York: The Macmillan Company, 1938.

This is a highly personalized story of an unusual life; it is written, however, from a somewhat detached point of view. It will interest those who are concerned with the psychologic effects of adverse early experience, and it should be read by those who have followed the scientific contributions of Dr. Jackson, especially by all who have any interest in esophagoscopy and bronchoscopy and the history of their development. In spite of his prolific medical writings, little has been known of the personal life of Dr. Jackson. In this autobiography he gives the salient facts of his career in a forthright and dispassionate manner, telling the story simply but well and revealing a character that one can almost imagine he himself had never found time to contemplate.

The recital of the conquest of frailty and ill health is almost heroic. Three active attacks of tuberculosis required treatment, in spite of such poverty that the ambitious medical student was forced to fill his own scant needs in an attic bedroom. Even more grippingly is shown the emergence of a fine character with high ideals, unselfishness, equanimity, patience and forebearance from early persecutions at school that well might have made of poorer human material a warped and useless personality.

As a story of earlier years in American medicine the book is of considerable interest. Especially enlightening is the description of the development of the craftsmanship and the ingenuity that led to Dr. Jackson's great contribution to endoscopy.

Sage advice is given on numerous subjects, for instance, the delivery of medical talks, the preparation of papers, the training of assistants, which has been one of Dr. Jackson's great pleasures, and the attainment of cooperation with medical staffs.

In places there is disclosed a certain sentimentality that one could almost consider a weakness if one did not know what a forceful character this physician has always shown and how much his humanity has done for sufferers, as in his successful campaign for the proper labeling of caustics.

One ends this enjoyable book with the feeling that he has learned to know a really great physician who has restated truly the satisfaction he has found in the practice and the achievements of medicine.

Bec-de-lèvre. By Victor Veau. Price, 100 francs. Pp. 326, with 1,214 illustrations. Paris: Masson & Cie, 1938.

This comprehensive monograph, written in collaboration with De Jaques Recamier, is a detailed clinical discussion and analysis of the surgery of cleft lip and cleft palate. It is profusely illustrated with line drawings and halftone reproductions of patients' photographs, which materially assist the text in presenting types of the deformity and the technic of the surgical procedures advocated.

The author has restricted his discussion almost entirely to the surgical aspects of the deformities. He has classified these defects as follows: (1) simple unilateral cleft lip, (2) total unilateral cleft lip, (3) simple bilateral cleft lip and (4) total bilateral cleft lip. These groups are further subdivided to include palatal defects. The first portion of the monograph is devoted to an analysis of the deformities, with a description of the characteristics of each division.

There follows a clinical discussion of the surgical treatment of each type of defect. The procedures are uniformly described in regard to current methods, personal experience and details of the author's technic. An outstanding feature is his manner of handling the incisions and suturing the lip. The many illustrations offer evidence of remarkably satisfactory results.

In a section dealing with the complications which follow operation Veau presents his method of handling these sequelae. He summarizes the optimum time of operation as follows: simple cleft lip, fourth week; total unilateral cleft lip, first operation at the end of the fourth week, second operation at the fifteenth month; total bilateral cleft lip, first operation, closing one side at the fourth week; second operation, closing the other side, at the fourth month; third operation, closing the palatal opening, at the fifteenth month.

The mortality in 1,210 cases was 12, or 2.1 per cent, in cases of total unilateral cleft lip; it was 10, or 4.9 per cent, in cases of total bilateral cleft lip. The operation on the palate raises the mortality appreciably, as indicated by the following statistics on this series: 9.4 per cent in the first year, 5.7 per cent in the second year, 2.7 per cent in the third year and 1.8 per cent in the fourth year.

The Treatment of Clinical and Laboratory Data. An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By Donald Mainland, M.B., Ch.B., D.Sc. Price, $15. Pp. 340, with 23 illustrations. Edinburgh: Oliver & Boyd, 1938.

Investigators of medical problems are turning more and more to mathematical developments of the theory of probability for reliable methods with which to evaluate the results of observation. Because the classic methods of statistical analysis are often not applicable to data derived from a small number of experiments, the worker concerned with such data must sooner or later study the writings of R. A. Fisher, who has furnished so many brilliant contributions to the statistical theories of small numbers. This book by Mainland should be regarded as a companion volume to R. A. Fisher's work (Statistical Methods for Research Workers, ed. 6, Edinburgh, Oliver & Boyd, 1936). It will be helpful to those who are studying medical problems because (*a*) the illustrative examples are drawn from the clinic and from the medical laboratory; (*b*) an appeal to understanding, rather than to esoteric mathematical derivations, is used in presenting the various formulas, and (*c*) the reader is repeatedly made aware that no type of computation can remove errors which arise from improper design of experiments. Adequate discussions are given of the following subjects: (1) the binomial expansion in estimating probability; (2) the chi-square test; (3) standard deviations, standard errors and the coefficient of variation; (4) methods for recording the errors of measurement, and (5) correlation. The subject of curve fitting is not considered in detail. Of special value is the method for calculating the error of measurement when the data consist of a series of duplicate observations.

The usefulness of the volume would have been enhanced by tables of chi-square, of areas under the normal curve, of t distributions and of z distributions. Without these tables the reader is compelled to consult other sources of information. It is difficult to believe that the tables were omitted because of copyright restrictions, since this book and its companion volume, by R. A. Fisher, are printed by the same publisher.

A Clinical and Genetic Study of 1,280 Cases of Mental Defect. By L. S. Penrose. Price, 12 shillings and 6 pence. Pp. 159, with 62 tables. London: His Majesty's Stationery Office, 1938.

This monograph summarizes an extremely careful and interesting study of 1,280 cases of mental defect which was carried out in England under the auspices of the Medical Research Council, the Darwin Trust and the Royal Eastern Counties Institution. The observations of the author were checked by other physicians. Psychologists and social workers took careful histories, made several home visits to each family and performed psychometric tests.

The author recognized that mental deficiency is a matter of degree and that an arbitrary line cannot be drawn between the normal and the abnormal. As each case was studied, special care was given to observation of physical abnormalities, neurologic signs, the family history, the social status and the mental status of the parents and of all available relatives.

There are many tables to indicate the number of cases and the degree of mental deficiency as correlated with each of the factors just cited. An appendix gives a summary of each case.

Some of the interesting conclusions are as follows: Only 7.6 per cent of the parents were mentally defective. Superior ability was twice as frequent among relatives of idiots as among relatives of the mentally defective higher grade, and idiocy was three times as frequent. There were 63 persons with mongolism, 95 per cent of whom came from normal parents. Cerebral trauma was given as a cause in but 23 of the cases.

This report is well written and should be read as a whole by any one who is interested in the etiology of mental defect.

Child Guidance Procedures. By Dr. Paul I. Schroeder, Director of the staff of the Institute for Juvenile Research. Price, $2.50. Pp. 362. New York: D. Appleton-Century Co., Inc., 1937.

The purpose of this book is to summarize the thinking and to explain the procedures, methods and technics which have been found fruitful at the Institute for Juvenile Research, Chicago.

There are a discussion of the types of cases studied at the clinic and a description of the various steps in the examination: taking the history, physical examination, psychologic tests, social investigation, the recreational interview and psychiatric study. Some of the common findings in each division are discussed, not with the idea of giving a complete exposition or contributing new ideas, but to illustrate the nature of the problems met at this clinic and the methods used in their solution.

Over a third of the book is devoted to illustrative cases, methods of therapy being pointed out. Finally, the relation of the clinic to the community and the need for the leadership given by a clinic are discussed. The individual physician —pediatrician or psychiatrist—receives little or no consideration in the scheme.

While the book was written primarily for those interested in child guidance clinics, it is also of value to physicians in pointing out the necessary steps in examination and the attitude to be assumed in studying problems of behavior.

The Psychology of Early Growth. By Arnold Gesell, M.D., and Helen Thompson, M.D., assisted by Catherine Strunk Amatruda, M.D. Price, $4. Pp. 290, with 30 illustrations. New York: The Macmillan Company, 1938.

"The present volume deals particularly with the biometric aspects of normative investigation." It describes growth in behavior from an objective point of view and deals with those factors which can be accurately measured.

The book is divided into three parts. Part 1 deals with methods and procedures; part 2, with norms of infants' growth, and part 3, with analytic appraisal of the status of growth. In addition, there are several appendixes.

There is a detailed description of methods of examination, including the exact procedure to be followed in examining behavior, and there is an accurate explanation of record taking. The tables indicate behavior norms for each test and measurement. There is a description of "maturity level summaries," which indicate the average age when a given behavior can be expected.

The authors hope that accurate objective descriptions of growth and behavior will bring the study of development of infants closer to the other biologic sciences. They feel that the processes of growth are comparable to embryologic development and may be analyzed genetically and in the same manner.

This book summarizes many years of investigations which Dr. Gesell and his associates have carried on at the Yale Clinic.

Pneumonia and Serum Therapy. By Frederick T. Lord, M.D., and Roderick Heffron, M.D. Revised edition. Price, $1. Pp. 148, with 10 illustrations and 10 tables. New York: The Commonwealth Fund, 1938.

In the present edition of this little book the authors have brought the text thoroughly up to date and have added much new material. Like the first edition, it is an authoritative, practical manual on the value and use of serum in cases of pneumonia. Theoretic aspects are outlined briefly. No clinician treating the disease can afford to be without a copy.

Stress is properly laid on the necessity of community or state programs for control of pneumonia in order to make serum available to all. The use of serum has been greatly hindered by the failure to appreciate this need. More extensive statistical data are included. These concern mortality rates, with and without serum therapy, for lobar pneumonia and bronchopneumonia, as well as the incidence

of the different types. The use of antipneumococcus rabbit serum is also discussed at some length. The data regarding the use of serum in older infants and older children are not satisfactory, but they are the best available.

Management of the Sick Infant and Child. By Langley Porter, M.D., and William E. Carter, M.D. Price, $10. Pp. 874, with 94 illustrations. St. Louis: C. V. Mosby Company, 1938.

The book is divided into three sections. In the first, each chapter has to do with a cardinal symptom, such as vomiting, diarrhea, constipation, hemorrhage, pain and tenderness, convulsions and syncopes, fever or cough. The significance of each of these various symptoms is considered, and treatment for the appropriate underlying condition is discussed. The second section comprises material found in the usual textbook. Diseases such as those of the respiratory tract, of the digestive tract and of the heart and circulation are discussed according to system. The last part of the book has to do with the various methods used in treating the sick infant and older child. There are also a chapter on formulas and receipts and one on drugs.

The material is well presented throughout. The illustrations are good, and the index is adequate.

A Guide to Mothers in Hawaii. By Joseph Palma, M.D. Pp. 135. Honolulu, Hawaii: Honolulu Star-Bulletin, 1938.

Dr. Palma's book is a delightful source of information for the mother during pregnancy and during the early life of her children. It is characterized by a thorough understanding of the subject, rare common sense and kindly humor. The necessary equipment for adequate care of the child is discussed in detail, as well as methods of maintaining hygiene and ways of meeting the nutritional requirements of the child. The short but adequate chapter on mental hygiene should prove particularly satisfactory; it is a counterbalance to the mass of unselected material on this subject which many mothers encounter. Chapters concerning the care of the sick baby, contagious diseases and traveling with a baby show the same emphasis on essential considerations. The book need not be confined to Hawaii, although it was written particularly for that territory.

The Infant. By Eric Pritchard. Price, $6. Pp. 744, with 47 illustrations. Baltimore: William Wood & Company, 1938.

This book covers the diseases of children who are in the first five years of life. There are a great number of textbooks on the diseases of infants, but this is unique in that it particularly concerns treatment. It contains little on pathology and etiology, nothing on prognosis and only enough on symptoms for the purpose of diagnosis. For each disease is described a method of treatment, to be used from the beginning to the end of the illness. The author explains that this one type of treatment is the best. Whether the reader agrees with him is immaterial. All of the various conditions of early childhood are thoroughly covered. For the busy practitioner who does not have time to judge between different schools of thought this book will be a blessing. It is written and printed well, and the illustrations are good.

A B C of the Vitamins. By Jennie Gregory, M.S. Price, $3. Pp. 105, with 56 charts. Baltimore: Williams & Wilkins Company, 1938.

This book pictures the various aspects of vitamins with charts. To my way of thinking it is effective and simplifies greatly this complicated subject. For teaching purposes it should be of much value. As a reference book it gives information readily though not in detail.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Sept. 9-12, 1940.
American Committee:
Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Kenneth Blackfan, 300 Longwood Ave., Boston.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St., W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.
Place: Frankfort on the Main, Germany. Time: June 12-18, 1938.

FOREIGN

British Paediatric Association

President: Dr. Hector C. Cameron, 23 Devonshire Pl., Upper Wimpole St., London, W. 1, England.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1, England.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen, Denmark.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen, Denmark.

Paediatrický Spolok na Slovensku

President: Dr. Pavel Radosa, Lazaretská 6, Bratislava, Czechoslovakia.
Secretary: Dr. S. Limbacher, Dlhá 2, Bratislava, Czechoslovakia.
Place: Pediatric Clinic, University, Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv, Palestine.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv, Palestine.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Sociedad Cubana de Pediatría

President: Dr. Clemente Inclan Costa, Manrique 48, Habana, Cuba.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana, Cuba.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Edward Clay Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Place: St. Louis. Time: May 15-19, 1939.

American Academy of Pediatrics

President: Dr. H. F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Region I. Place: Hotel Seneca, Rochester, N. Y. Time: Nov. 11-12, 1938.
Region II. Place: Skirven Hotel, Oklahoma City. Time: Nov. 16, 1938.
Region III. Place: Statler Hotel, Detroit, Mich., and Ann Arbor, Mich. Time: Oct. 27-29, 1938.

American Hospital Association, Children's Hospital Section

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

American Pediatric Society

President: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 27-29, 1939.

Canadian Society for the Study of Diseases of Children

President: Dr. Alton Goldbloom, 1543 Crescent St., Montreal.
Secretary-Treasurer: Dr. Pearl Summerfeldt, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. L. Emmett Holt Jr., Johns Hopkins Hospital, Baltimore.
Secretary: Dr. A. A. Weech, 3975 Broadway, New York.

SECTIONAL

North Pacific Pediatric Society

President: Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Charles E. Conrad, 209-210 Professional Bldg., Harrisburg, Va.
Secretary: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.
Place: Oklahoma City. Time: Nov. 15-18, 1938.

STATE

Alabama Pediatric Society

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.
Place: Montgomery. Time: April 17, 1939.

Arkansas State Pediatric Association

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.
Place: Hot Springs. Time: January 1939.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.

Florida State Pediatric Society

President: Dr. Gilbert S. Osincup, 300 E. Colonial Dr., Orlando.
Secretary: Dr. Warren W. Quillian, 227 Avenue Aragon, Coral Gables.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. Charles Hall Farmer, 553 Walnut St., Macon.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.
Scientific Meeting—Place: Augusta. Time: December 1938.
Business Meeting—Place: Atlanta. Time: April 1939.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. J. Harold Root, 103 N. Main St., Waterbury.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Indiana State Pediatric Society

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Ruth Aleman, 1407 S. Carrollton Ave., New Orleans.
Secretary-Treasurer: Dr. Philip C. de Verges, 312 Audubon Bldg., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 842 Park Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John P. Scott, 1740 Bainbridge St., Philadelphia.
Secretary: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.
Place: Detroit. Time: Sept. 20-22, 1938.

Mississippi State Pediatric Society

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. J. A. Henske, 1614 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. J. H. Murphy, 915 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. John LaBruce Ward, Arcade Bldg., Asheville.
Secretary: Dr. Lewis Elias, 36 Grove St., Asheville.

Oklahoma State Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

South Carolina Pediatric Society

President: Dr. Mylnor W. Beach, 126 Meeting St., Charleston.
Secretary-Treasurer: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.

Tennessee State Pediatric Society

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Place: Jackson. Time: April 11, 1939.

Texas Pediatric Society

President: Dr. F. O. Calaway, 3306 Fannin St., Houston.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Houston. Time: May 9, 1939.

Virginia Pediatric Society

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.
Place: Danville, Va. Time: October 1938.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

Bronx Pediatric Society

President: Dr. Samuel Tripler, 1555 Grand Concourse, New York.
Secretary: Dr. Harry S. Altman, 940 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank Vasder Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

Chicago Pediatric Society

President: Dr. Joseph K. Calvin, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. W. H. Bradford, 1719 Pacific Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3622 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140 Second Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. L. H. Goldsmith, 384 Peachtree St., N. E., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. John K. Glen, 4412 Montrose Blvd., Houston, Texas.
Secretary-Treasurer: Dr. J. L. Collier, 1620 Medical Arts Bldg., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

Kansas City (Missouri) Pediatric Society

President: Dr. W. R. Moore, 620 Francis St., St. Joseph, Mo.
Secretary: Dr. F. S. Hogue, 1103 Grand Ave., Kansas City, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif..
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sidney D. Kramer, 61 Eastern Parkway, Brooklyn.
Secretary: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: Third Wednesday of each month, October to May.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. Joseph Shimpa, 2309 N. 36th St., Milwaukee.
Secretary: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New England Pediatric Society

President: Dr. Hyman Green, 483 Beacon St., Boston.
Secretary-Treasurer: Dr. Henry E. Gallup, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Lucy Porter Sutton, 168 E. 74th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northwestern Pediatric Society

President: Dr. Roger L. J. Kennedy, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

Philadelphia Pediatric Society

President: Dr. Julian M. Lyon, 40 Llanfair Rd., Ardmore, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

Richmond Pediatric Society

President: Dr. A. S. Hurt, 1028 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. Louise Fry Galvin, 2416 Stuart Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month (except July, August and September).

Rochester Pediatric Society

President: Dr. J. Merrel Parker, 11 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

Rocky Mountain Pediatric Society

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

St. Louis Pediatric Society

President: Dr. John Zahorsky, 536 N. Taylor Ave., St. Louis.
Secretary-Treasurer: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

Seattle Pediatric Society

President: Dr. Walter B. Seelye, 1305–4th Ave., Seattle.
Secretary: Dr. Armin Rembe, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Philip E. Rothman, 3875 Wilshire Blvd., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Damon O. Walthall, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. Norman Survis, 650 Main St., New Rochelle, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye, N. Y.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.